In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-515V

Filed: November 16, 2022

ELIZABETH GRAM, *for and on behalf of her minor daughter,* A.L.M.,	*	To Be Published
Petitioner,	*	Ruling on Entitlement; Afebrile Seizures; Epilepsy; DTaP, Hib, MMR, Prevnar 13, Varicella Vaccines; Insufficient Proof of Causation.
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Sean Greenwood, Esq., Greenwood Law Firm, Houston, TX, for petitioner.
Christine Becer, Esq., U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Roth, Special Master:

On May 19, 2015, Elizabeth Gram ("Ms. Gram" or "petitioner") filed a petition on behalf of her minor child, A.L.M., for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, et seq.[2] (the "Vaccine Act" or "Program"). The petition alleges that A.L.M. received DTaP, Hib, MMR, Pneumococcal conjugate, and Varicella vaccinations on October 25, 2012 and thereafter developed a seizure disorder. Petition at 1, ECF No. 1.

An entitlement hearing was held on November 23, 2020 via videoconferencing. Following careful review and analysis of all the documentary evidence and testimony submitted in this case

[1] This Decision has been designated "to be published," which means I am directing it to be posted on the Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). **This means the Decision will be available to anyone with access to the internet.** However, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Decision will be available to the public. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

by both petitioner and respondent and in accordance with the applicable legal standards, I find that petitioner has not proffered sufficient evidence to demonstrate that the vaccinations A.L.M. received on October 25, 2012 caused or contributed to her afebrile seizure disorder. Accordingly, I find that petitioner is not entitled to compensation.

I. Issues to be Determined

The parties dispute whether any of the vaccines A.L.M. received on October 25, 2012 can cause afebrile seizures and epilepsy, and, if so, whether the vaccines caused A.L.M.'s injury here. Thus, all three *Althen* prongs are at issue.

II. Procedural History

Ms. Gram filed the petition on May 19, 2015, and her case was initially assigned to Special Master Nora Beth Dorsey. Pet. Ex. 1, ECF No. 1. Petitioner filed medical records in the form of compact discs on the following dates: July 7, 2015, March 8, 2016, and June 14, 2016. On October 21, 2015, the case was reassigned to the undersigned. ECF No. 15. Petitioner filed additional medical records on the following dates: March 4, 2016, August 8, 2016, August 7, 2017. Pet. Ex. 13, 15, 19, and 20, ECF Nos. 23, 33, and 46.

Petitioner filed expert reports from Dr. Marcel Kinsbourne on August 8, 2016, Pet. Ex. 14, ECF Nos. 35, 41, and 91; on March 13, 2017, Pet. Ex. 16, ECF Nos. 42 and 91; on September 7, 2017, Pet. Ex. 21, ECF. Nos. 49 and 91; and on April 16, 2018, Pet. Ex. 36, ECF Nos. 53 and 91.

Petitioner also filed expert reports from Dr. Alan Levin on September 24, 2018, Pet. Ex. 39, ECF No. 62; and on May 20, 2019, Pet. Ex. 50, ECF No. 80.

In support of petitioner's expert reports, petitioner filed medical literature on September 7, 2017, Pet. Ex. 22-35, ECF No. 49; on April 16, 2018, Pet. Ex. 37, ECF Nos. 53 and 91; on August 17, 2018, Pet. Ex. 37 and 38, ECF No. 58; on September 24, 2018, Pet. Ex. 41-45, ECF No. 63; on June 26, 2019, Pet. Ex. 51-55, ECF No. 81; on October 13, 2020, Pet. Ex. 58, ECF No. 100; and November 17, 2020, Pet. Ex. 59-61, ECF No. 105.

Respondent filed expert reports from Dr. Gregory Holmes on November 8, 2016, Resp. Ex. A, ECF No. 37; on December 29, 2017, Resp. Ex. Q, ECF No. 51; on June 15, 2018, Resp. Ex. V, ECF No. 55; and on August 16, 2019, Resp. Ex. YY, ECF No. 82.

Respondent also filed expert reports from Dr. Christine McCusker on December 21, 2018, Resp. Ex. Z, ECF Nos. 73 and 75; and on August 16, 2019, Resp. Ex. FFF, ECF No. 82.

In support of the expert reports, respondent filed medical literature on December 8, 2016, Resp. Ex. C-P, ECF No. 38; on December 29, 2017, Resp. Ex. R-U, ECF No. 51; on June 15, 2018, Resp. Ex. W-Y, ECF No. 55; on April 17, 2019, Resp. Ex. BB-XX, ECF Nos. 78 and 79; and on August 16, 2019, Resp. Ex. ZZ, AAA-EEE, GGG, and HHH, ECF No. 82.

An entitlement hearing was held on November 23, 2020 via videoconferencing. Both

parties filed post-hearing briefs on March 11, 2021, and petitioner filed a reply brief on January 14, 2022. See ECF Nos. 109, 110, and 111.

This matter is now ripe for decision.

III. Relevant Medical Terminology

The following medical terms appear throughout this decision.

A **seizure** is defined as the sudden attack or recurrence of a disease or the single episode of epilepsy.[3] It involves a temporary, uncontrolled surge of electrical activity in the brain.[4] Multiple seizures occurring in a 24-hour period are considered a single event.[5]

A **focal seizure**, also known as a "partial" seizure, is a seizure that occurs in a specific part of the brain, although the surge of electrical activity can move from one location to another as the seizure intensifies.[6] These seizures are most common in people with head injuries, febrile childhood seizures, brain infections, or other conditions that affect the brain.[7]

A **complex partial seizure** is a partial seizure characterized by varying degrees of impairment of consciousness; the person affected performs non-purposeful, repetitive movements which they may not remember.[8]

A **provoked seizure** is a seizure that is the result of environmental stress, such as low blood sugar, low blood sodium, fever, alcohol or drug withdrawal, or an infection that does not usually affect the brain. [9] Tr. 141. On the other hand, an **unprovoked seizure** occurs without a concurrent illness, fever, or acute brain injury.[10]

Epilepsy is characterized by paroxysmal transient disturbances of brain function that may manifest as loss of consciousness, abnormal motor phenomena, sensory disturbances, or perturbation of the autonomic nervous system.[11] It is considered one of the most common nervous system disorders.[12]

Mesial temporal sclerosis is scarring in the inner portions of the temporal lobe. It may be caused by brain infection or head trauma that interrupts the flow of oxygen to the temporal lobe,

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[3] *Dorland's Illustrated Medical Dictionary* 1660 (33rd ed. 2019) [hereinafter "*Dorland's*"].
[4] Cleveland Clinic, *Seizure*, https://my.clevelandclinic.org/health/diseases/22789-seizure.
[5] Wei-Ling Lee, MD & Hian-Tat Ong, MD, *Afebrile Seizures Associated with Minor Infections: Comparison with Febrile Seizures and Unprovoked Seizures*, 31 PEDIATRIC NEUROLOGY 157, 158 (2004), filed as "Pet. Ex. 29."
[6] Cleveland Clinic, *Focal Seizure*, https://my.clevelandclinic.org/health/diseases/22893-focal-seizure.
[7] *Id.*
[8] *Dorland's* 1660.
[9] Lee & Ong, *supra* note 5.
[10] *Id.*
[11] *Dorland's* 626.
[12] Johns Hopkins Medicine, *Epilepsy: Overview*, https://www.hopkinsmedicine.org/health/conditions-and-diseases/epilepsy.

resulting in brain cell death. It can cause a form of temporal lobe epilepsy with partial (focal) seizures that can spread and affect other areas of the brain.[13]

Encephalopathy is any degenerative disease of the brain that alters brain function or structure.[14] Abnormal results from cerebrospinal fluid ("CSF") may show encephalopathy.[15]

Landau-Kleffner Syndrome is an epileptic syndrome of childhood characterized by partial or generalized seizures, psychomotor abnormalities, and aphasia progressing to mutism.[16]

IV. The Factual Record

A. A.L.M.'s Medical History Prior to the Vaccinations

A.L.M. was born on October 24, 2011. Pet. Ex. 14. Apart from being slightly jaundiced at birth, A.L.M. was the product of an uncomplicated term pregnancy. Pet. Ex. 10 at 5; Pet. Ex. 14 at 3. She received a Hepatitis B vaccination on the day she was born. Pet. Ex. 10 at 7, 9. She was discharged home with her mother on October 26, 2011. Pet. Ex. 11 at 221-37; Pet. Ex. 10 at 5-10.

A.L.M. was presented for follow up examinations of neonatal jaundice on October 27, 2012 and October 29, 2012. Pet. Ex. 11 at 196, 219-22.

A.L.M. had some feeding difficulties in the first month of life that resolved without event. Pet. Ex. 11 at 181-82, 191-92, 194.

On November 29, 2011, at five weeks old, A.L.M. was presented to the pediatrician with acute respiratory infection, congestion, and spitting up. Pet. Ex. 11 at 175. A.L.M. was gasping at times, seemed unable to breathe, and had not slept well the night prior; she tested positive for respiratory syncytial virus ("RSV"). *Id.* at 176-77, 179.

At a follow up examination on December 2, 2011, A.L.M.'s physician noted that she had acute bronchiolitis due to RSV with eyes tearing, loss of appetite, ear problem, increased congestion, and coughing. Pet Ex. 11 at 167-68, 170-72. Petitioner was instructed to use a humidifier, saline drops, and a bulb syringe. *Id.* at 172. At follow up on December 8, 2011, A.L.M. was improving with an increased appetite, but she had a raspy cry. *Id.* at 167.

At her two-, four-, and six-month-old well baby visits, A.L.M. was meeting all milestones. Pet. Ex. 11 at 146-48, 151-54, 158-61. On January 13, 2012, she received Pediarix (a combination vaccine which includes DTaP, Hepatitis B and polio) and Hib vaccinations; petitioner declined

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[13] Johns Hopkins Medicine, *Epilepsy Causes*, https://www.hopkinsmedicine.org/health/conditions-and-diseases/epilepsy/epilepsy-causes.

[14] *Dorland's* 608; National Institute of Neurological Disorders and Stroke, *Encephalopathy*, https://www.ninds.nih.gov/health-information/disorders/encephalopathy.

[15] T. Ichiyama et al., *Tumor Necrosis Factor-[alpha], interleukin-1[beta], and interleukin-6 in Cerebrospinal Fluid from Children with Prolonged Febrile Seizures: Comparison with Acute Encephalitis/Encephalopathy*, 50 AM. ACAD. OF NEUROLOGY 407 (1998), filed as "Pet. Ex. 42."

[16] *Dorland's* 1806.

Prevnar and Rotateq at this visit. *Id.* at 161. On March 6, 2012, A.L.M. received Hib, Pediarix, and Prevnar 13 (a pneumococcal vaccine that protects against bacterium Streptococcus pneumoniae) vaccinations. *Id.* at 155. On April 25, 2012, she received Pediarix and Prevnar 13. *Id.* at 150. A.L.M. received all the above vaccinations without event.

On June 5, 2012, A.L.M. was presented to the pediatrician after rolling off the bed and hitting her head on the carpeted floor. Pet. Ex. 11 at 141. Her mother reported a bump on her forehead. *Id.* Petitioner also reported that A.L.M. had rolled off the bed earlier in the week as well and was found on her belly. *Id.* A.L.M. cried a bit but was laughing later. *Id.* She had no vomiting, was acting fine, and was using all extremities. *Id.* The physician noted that A.L.M. had a possible bump on the right side of her forehead. *Id.* at 142.

On July 24, 2012, at her nine-month-old well baby check, A.L.M. was meeting all milestones and had a normal checkup. Pet. Ex. 11 at 86-90, 137, 139.

On August 21, 2012, A.L.M. was presented to the emergency room ("ER") at Memorial Hermann Southeast Hospital ("Memorial Hermann") with vomiting, diarrhea, and fever since the night before. Pet. Ex. 7 at 141. An abdominal X- ray showed gaseous distention of the stomach and portions of the small and large bowel with multiple air fluid levels on upright view. *Id.* at 142. The physician noted that the findings were "not normal" and may be related to adynamic ileus or a small bowel obstruction. *Id.* at 142, 145. Petitioner left with A.L.M. before the results were discussed and before discharge papers were given. *Id.* at 143. The discharge notes indicated that A.L.M. was in good and stable condition. *Id.*

A.L.M. was presented to the pediatrician the next day with a two-day history of vomiting, diarrhea, and decreased appetite. Pet. Ex. 11 at 129. Petitioner advised that she took A.L.M. home before receiving any test results from the ER because A.L.M. had a large bowel movement. *Id.* at 130. Petitioner also noted that A.L.M.'s diaper was dry this morning, and she seemed perkier. *Id.* at 129-31. The physician's assessment was that A.L.M. had colitis, enteritis, and gastroenteritis of infectious origin. *Id.* at 129.

On October 25, 2012, at her one-year-old checkup, A.L.M. was meeting all milestones. Pet. Ex. 11 at 120-21. At this point, she was walking 2-3 steps independently, drinking from a cup, babbling with inflection, and playing simple games (peek-a-boo and pat-a-cake). *Id.* at 121. A.L.M. received her DTaP, Hib, MMR, Prevnar 13, and Varicella vaccinations, but petitioner declined the Influenza vaccine. *Id.* at 122.[17]

[17] At the October 25, 2012 checkup, petitioner was provided with a fact sheet associated with the vaccines A.L.M. received that day, which included in pertinent part:

> A small number of children get a rash and fever 7 to 14 days after the measles-mumps-rubella (MMR) or the varicella vaccines. The rash is usually on the main body area and lasts 2 to 3 days. Call your healthcare provider within 24 hours if the rash lasts more than 3 days or gets itchy. Call your child's provider **immediately** if the rash changes to purple spots.

Pet. Ex. 11 at 122, 127 (emphasis in original).

B. A.L.M.'s Medical Records after the Vaccinations

A.L.M.'s next medical visit was on November 26, 2012, when petitioner brought her in for "possible seizure activities." Pet. Ex. 11 at 115-16. Petitioner reported that A.L.M. was having staring episodes with chewing motions starting about one week prior. *Id.* at 116. A.L.M. was noted to be sitting during the episodes. *Id.* A.L.M. reportedly had two episodes on November 25, 2016, the day before petitioner brought her in to be seen, which also involved twitching of the left eye. *Id.* She had an episode the day of the appointment with staring and movement of her tongue and left fingers for about 4 seconds. *Id.* The progress notes stated that she did not drool and had no injuries, trauma, URI symptoms, or fever. *Id.* The pediatrician's assessment was "staring spell; suspect seizure activity." *Id.* The pediatrician made a referral for an electroencephalogram ("EEG") and a neurology appointment with Dr. Dreyer. *Id.* at 116, 118. A.L.M. had an EEG on November 29, 2012 that was "normal in wake and sleep." *Id.* at 238.

Petitioner telephoned the pediatrician on December 1, 2012.[18] Pet. Ex. 4 at 2.

The next day, December 2, 2012, A.L.M. was presented to Texas Children's Hospital ("TCH") with a history of "having sz like episodes" beginning 4-6 weeks prior. Pet. Ex. 15 at 2. Petitioner reported that A.L.M. would stare, left eye twitching, lips smacking, and not responding to her name during the episodes. *Id.* There was no associated body shaking or stiffness, but she seemed to be losing her balance more in the past week. *Id.* Initially, the episodes lasted 10-15 seconds and occurred twice daily, but now lasted 30-45 seconds and occurred 4-5 times daily. *Id.* Petitioner reported five episodes that day. *Id.* A.L.M. was otherwise healthy and meeting all milestones. *Id.* Petitioner reported that A.L.M. was seen by a neurologist last week and had a 30-minute EEG that was normal. *Id.* Petitioner was told to follow up with the primary care physician. *Id.* A.L.M. was noted to be "negative for fever" and "positive for seizures." *Id.* at 2, 3. The record documented a "[H]istory consistent with possible complex partial seizure, asymptomatic currently. Okay for outpatient workup." *Id.* at 4. Discharge instructions were to schedule an EEG and discuss an outpatient Magnetic Resonance Imaging ("MRI") to be done by the primary care physician. *Id.*

The following morning, December 3, 2012, A.L.M. was presented to the pediatrician. Pet. Ex. 11 at 111; Pet. Ex. 4 at 3. The pediatrician ordered an MRI without contrast and issued a referral for Dr. Dreyer in neurology and EEG/EP. Pet. Ex. 11 at 45, 112. Petitioner was instructed to go to the ER if A.L.M.'s condition worsened. *Id.* at 112.

On December 3, 2012, around 7pm, A.L.M. was presented to the ER at Memorial Hermann for seizure onset at about 3:30pm. Pet. Ex. 7 at 157. She reportedly had three seizures that day but was awake and alert on presentation. *Id.* at 157, 159. A.L.M.'s vitals were taken, and her temperature was 98.8 degrees Fahrenheit. *Id.* at 157. Petitioner reported that the seizures began one month ago and were getting worse. *Id.* at 171. The seizures lasted seconds with no loss of consciousness and no confusion postictally. *Id.* Petitioner stated that A.L.M.'s first episode occurred while A.L.M. was playing and crawling and then she sat up and made chewing motions for approximately ten seconds; this occurred twice. *Id.* at 2. In later episodes, her left eye started to twitch, then her eyes moved back and forth slowly from left to right; additionally, in more recent

[18] The phone log does not contain any content other than a date.

episodes, both hands shook, and she made a chewing motion. *Id.* A.L.M. did not respond to her name during the episodes. *Id.* After the episodes, she briefly appeared tired before returning to baseline. *Id.* Petitioner reported that A.L.M. had these episodes 4 to 5 times per day. *Id.* A.L.M. had an episode during this ER visit that lasted for about one minute. *Id.*

The notes indicated that A.L.M. was seen three days ago at TCH ER, at which time neither an EEG or MRI was performed, and no medication was started. Pet. Ex. 7 at 2; Pet. Ex 10 at 67. The physician noted that A.L.M. was afebrile but positive for diarrhea, which had now resolved. Pet. Ex. 7 at 16. She was walking, said "momma," and knew her name. *Id.* at 17. There were no developmental delays. *Id.* Petitioner herself was noted to have a history of febrile seizures at age three but does not have epilepsy, and A.L.M.'s paternal half uncle has epilepsy. Pet. Ex. 7 at 17; Pet. Ex. 10 at 82. The physician concluded that A.L.M. had an unprovoked seizure, was developmentally normal for her age, and had multiple nonfebrile tonic and clonic seizures. Pet. Ex. 7 at 18. There was no overt perinatal insult identified. *Id.*

On December 4, 2012, A.L.M. was transferred from Memorial Hermann to Children's Memorial Herman Hospital ("CMHH"). Pet. Ex. 7 at 175-76; Pet. Ex. 10 at 81. The same day, petitioner called the pediatrician.[19] Pet. Ex. 4 at 3. A 23-hour EEG at CMHH showed a seizure unofficially read as temporal lobe epilepsy more prominent on left. Pet. Ex. 7 at 2-3, 21-22, 33-34; Pet. Ex. 10 at 71-72. She also had a brain MRI, the results of which were normal. Pet. Ex. 7 at 80; Pet. Ex. 10 at 84. Complete blood count ("CBC") results showed a right shift to be monitored for fever or signs of infection. Pet. Ex. 7 at 18, 180-81. While in the hospital, a urine analysis was abnormal. *Id.* at 182. A.L.M. had multiple seizure events during her two-day hospitalization. Pet. Ex. 10 at 85. She was discharged on December 6, 2012 with a prescription for Keppra and Diazepam for seizures greater than 10 minutes. Follow up was recommended. Pet. Ex. 7 at 21-22. The diagnosis was likely temporal lobe epilepsy. *Id.* at 21.

Petitioner called the pediatrician on December 7, 2012 and presented that day for follow up. Pet. Ex. 4 at 3; Pet. Ex. 11 at 108. Petitioner reported that A.L.M. was diagnosed with complex partial seizures and prescribed Keppra; petitioner noted that A.L.M. was doing well with no seizures since her hospital discharge the day before. Pet. Ex. 11 at 106, 108. Her neurologist at the hospital was Dr. Butler. *Id.* at 109.

A.L.M. continued to do well until she reportedly had five seizures between December 25 and 26, 2012. Pet. Ex. 7 at 222-79. She was admitted to CMHH for generalized epileptic seizures. *Id.* at 227. Tests performed earlier that month showed left temporal lobe epilepsy on a video-electroencephalogram ("vEEG") and a normal brain on the MRI. *Id.* at 22, 270. Her initial seizures included staring, chewing motions, then left eye twitching; current seizures included collapsing with more involvement of bilateral extremities lasting 1 to 1.5 minutes. *Id.* at 2, 210. She was on "300 mg po BID" of Keppra daily and taking it as recommended. *Id.* at 225, 270. Multiple seizures were reported with no post ictal phase. *Id.* at 225. She was scheduled to see Dr. Heard, a pediatric epileptologist, on January 8, 2013. *Id.* at 197, 199, 272. She was discharged on December 28, 2012 with a plan to continue weaning her off Keppra and adding Trileptal. *Id.* at 209, 272.

[19] The records only show that a call was made to the pediatrician's office on that date.

A.L.M. was presented to the pediatrician on January 2, 2013 with a respiratory infection for two days. She was noted to have complex partial epilepsy. Pet. Ex. 11 at 105. She was in the process of weaning off Keppra and switching to Trileptal. *Id.* Since starting Trileptal, she had no further seizures. *Id.*

A.L.M. was presented to neurologist Dr. Heard on January 8, 2013. Pet. Ex. 10 at 64. A.L.M.'s seizures reportedly began a month prior to her first hospitalization with staring and lip smacking which increased over the next several weeks with left eye twitching and left hand twitching. *Id.* A 23-hour EEG performed during her early December hospital stay showed left temporal epileptiform activity. MRI was normal. *Id.* A.L.M. was discharged from the hospital on December 6, 2012 with a prescription for Keppra. *Id.* Despite the prescription, her seizures continued, and now involved her entire body with bowel incontinence. *Id.* The Keppra prescription was increased to maximum without success. *Id.* A.L.M. was again admitted to the hospital on December 25, 2012, weaned off Keppra and prescribed Trileptal. *Id.* While being weaned from Keppra and switched to Trileptal, A.L.M. was seizure-free for four days. *Id.* However, while at Dr. Heard's office, she had a seizure that lasted 25 seconds with a few clonic hand jerks, left eye twitching, and blue lips and mouth. *Id.* at 66. The entire episode lasted 45-60 seconds. *Id.* A.L.M. "spaced out" for about 5 seconds afterwards then continued eating her snack. *Id.* Dr. Heard increased the Trileptal, ordered a helmet, and instructed petitioner to follow up in 1-2 months. *Id.*

At her 16-month-old well child visit on March 15, 2013, A.L.M. was noted to have a past diagnosis of complex partial seizure and was taking Trileptal. Pet. Ex. 11 at 100. There were no current health problems or concerns. *Id.* A.L.M. was reaching all milestones, walking independently, and had 4-6 words. *Id.* Petitioner declined vaccinations. *Id.* at 100-01.

On the 18-month Ages & Stages Questionnaire ("ASQ")[20] petitioner noted concern about A.L.M.'s speech delay and "the fact that seizures began within 2 weeks of 12 month vaccination." Pet. Ex. 2 at 6.

Over the next several months, A.L.M. was presented with multiple febrile illnesses including: April 1, 2013 for viral gastroenteritis with a four-day fever of 102 degrees Fahrenheit, Pet Ex. 11 at 92-93; April 12, 2013 for otitis media, URI with fever upon presentation, a "terrible" runny nose, vomiting with cough and "banging her head on the wall" for 1-2 weeks, Pet. Ex. 11 at 84-85; and May 14, 2013 for Hand, Foot and Mouth disease with 103.2 fever. Pet. Ex. 11 at 212-13. A.L.M. had no seizures from any of these febrile illnesses.

At her neurology visit with Dr. Heard on June 3, 2013, A.L.M.'s last seizure was noted to be on February 4, 2013. Pet. Ex. 10 at 50. Her seizures were under control with Trileptal. *Id.* at 51. A.L.M. was noted at this visit to have a speech impediment and that the left temporal lobe epilepsy could be playing a part in her speech difficulties. *Id.* She was diagnosed with Landau Kleffner syndrome, although she did not have the typical symptoms and features. *Id.* Dr. Heard prescribed speech therapy, as well as Lamictal to help with A.L.M.'s language development. *Id.* Petitioner was encouraged to bring A.L.M. up to date on her immunizations, but she expressed concern "about the coincidence of seizures occurring within weeks of her 1 yr immunizations." *Id.*

[20] The form does not contain a date.

Thereafter, A.L.M. was presented for medical care on July 11, 2013 for sinusitis and drainage and redness of her eyes without fever, Pet. Ex. 11 at 75; September 8, 2013 for periorbital cellulitis, Pet. Ex. 11 at 24; September 9, 2013 for eye swelling, acute upper respiratory infection, and acute otitis media, Pet. Ex. 11 at 70; and September 12, 2013 for a follow up from the last appointment, at which time she was doing well. Pet. Ex. 11 at 66.

At her well child visit on September 16, 2013, A.L.M. had ear pulling, no fever, good appetite and had reached all milestones appropriate for her age. Pet. Ex. 11 at 56-57. She could run, scribble spontaneously with a crayon, had 7 to 10 words, and imitated use of objects (for example, using a comb and a phone). *Id.* at 57. An M-Chat was completed with no concerns noted. *Id.* at 57-58. However, speech delay was noted on ASQ survey, so petitioner was instructed to contact Early Childhood Intervention ("ECI") for speech services. *Id.* at 59. Petitioner again declined vaccinations for A.L.M. *Id.*

An occupational therapist and intervention specialist performed an ECI Assessment for A.L.M. at petitioner's home on October 1, 2013. Pet. Ex. 10 at 17-32. The comments noted that A.L.M. "has a diagnosis of seizure disorder, which automatically qualifies her for ECI enrollment," and "mom's primary concern developmentally is communication." *Id.* at 17.

At a follow up visit on October 8, 2013, Dr. Heard documented a 19-month-old whose seizures were controlled on Trileptal; A.L.M. had not had a seizure since February 4, 2013. Pet. Ex. 10 at 43. Petitioner reported numerous URIs and viral illnesses since starting day care in March. *Id.* She was concerned about A.L.M.'s communication skills since she could only pronounce a few words and her vocabulary was limited. *Id.* A.L.M. had been evaluated by a speech therapist, but the therapy had not yet started. *Id.* She had a diagnosis of Landau Kleffner syndrome, though she did not have the typical symptoms. *Id.* at 45. Dr. Heard again suggested that Lamictal be started to reduce the spikes in the temporal lobe and improve neuronal development for language; petitioner was "more amenable today to give the Lamictal a try." *Id.* at 45.

Genetic testing for chromosomal microarray analysis performed on October 8, 2013 was negative.[21] Pet. Ex. 10 at 47.

On June 3, 2014, A.L.M. was presented to the pediatrician for herpangina, an infection in the back of the throat. Pet. Ex. 11 at 52. She was a two-year-old with a three-day fever, a slight cough the day before, and a sore throat the night prior. *Id.* Her current medication was listed as Trileptal. *Id.* Petitioner was advised to encourage fluids and give Tylenol or ibuprofen as needed. *Id.* at 53.

In October 2014, an initial evaluation at the Westwood Elementary School was performed for an Individual Education Program ("IEP") Report. Pet. Ex. 5 at 1. A.L.M. was nearly three years old. *Id.* at 2. She attended daycare three days a week. *Id.* at 18, 23. Her primary disability was "Speech Impairment" with articulation as the main concern. *Id.* at 5-7. Speech Language Therapy for fourteen 30-minute sessions over nine weeks was recommended to begin on October 24, 2014. *Id.* at 16. Her history was seizures controlled with medication and no seizures since February 2013.

[21] The record is incomplete. The document filed contains only a description of chromosomal microarray analysis. *See* Pet. Ex. 10 at 47.

Id. at 20. She lived with her mother, stepfather, and 12-year-old sister. *Id.* at 23. She was the product of an uneventful pregnancy and delivery with normal childhood illnesses until two weeks after her 12-month vaccinations, at which time she began having seizures. *Id.* at 24. She was hospitalized and diagnosed with epilepsy, complex partial seizures with secondary generalization. *Id.* Petitioner reported no issues with word development until after her seizures began, after which time she went months without progress in her speech. *Id.* Petitioner believed that A.L.M.'s speech was affected by the type of seizures she experienced. *Id.* at 24, 42. Her hearing, vision, and motor skills were normal. *Id.* at 24. A.L.M. was well behaved and responded appropriately to discipline. *Id.* The report also said that A.L.M. separated well from her mother, played by herself, and was agreeable and happy. *Id.* at 25. A.L.M. scored within the average range for receptive, expressive, and total language; further, "no concerns were raised regarding her language development." *Id.* She used primarily "d," "t," and "b" in substitution, placing her in the 3rd percentile below the criteria used to determine an articulation disability. *Id.* at 26. Her language, voice, and fluency skills were intact. *Id.* at 27.

Petitioner filed a request for exemption of vaccinations with the Texas Department of State Health Services on October 29, 2014. Pet. Ex. 3.

At a March 26, 2015 neurology visit, A.L.M. was taking Trileptal two times daily, and was making "good progress" in speech therapy in both her language and speech. Pet. Ex. 10 at 38. Her last seizure was on February 4, 2013 and last EEG was in 2012. *Id.* at 37. Petitioner gave A.L.M. one dose of Lamictal but stopped it because A.L.M. fell and petitioner felt that Lamictal made her unsteady. *Id.* at 38, 39. She had not received vaccinations since October 2012 because petitioner believed that the vaccines triggered her seizures. *Id.* at 38. A.L.M. attended daycare three days a week and stayed with her aunt or grandmother on the other days. *Id.* She liked to play with dolls, Legos, and coloring books. *Id.* She was affectionate and had good eye contact, with no other behaviors suggestive of autism spectrum disorder ("ASD"). *Id.* The record documented onset of seizures at 13 months of age with no trigger. She had no further seizures since February 4, 2013; the seizure type included staring spells and lip smacking lasting 10 seconds 4-5 times a day. *Id.* at 39. It was also noted that her paternal half uncle has epilepsy. *Id.* A 23-hour EEG done on December 4, 2012 was abnormal "due to bihemispheric multifocal independent epileptiform discharges, more prominent in the left hemisphere, particularly the temporal area, and 1 electrographic seizure that appeared to arise from the left temporal area." *Id.* at 40. Her brain MRI done the same day was normal. *Id.* The assessment was a three-year-old on Trileptal, seizure free for two years since February 2013, with speech impairment improved. *Id.* Before considering weaning her off medication, the physician wanted another EEG and repeat brain MRI to evaluate myelination. *Id.* at 40-41.

A chromosomal microarray analysis – HR + SNP screen performed on March 27, 2015 was normal. Pet. Ex. 6 at 1. A 23-hour video and scalp EEG done on July 5, 2015 was normal for her age. Pet. Ex. 19 at 6. The brain MRI without contrast was performed on August 27, 2015 and compared to the December 2012 MRI; results were negative and normal with no migrational anomaly or focal cortical dysplasia. *Id.* at 107.

A.L.M.'s assessment for the 2016-2017 school year was speech impairment in the area of articulation. Pet. Ex. 20 at 4, 26. The notes document that A.L.M. "no longer takes medication for

seizures. Mom reports she has been off of the medication for about a year." *Id.* at 5. A.L.M. was noted to need only speech services and could enter kindergarten with no need for accommodations. *Id.* at 26.

C. Other Evidence

i. VAERS report

Two years post-vaccination, petitioner completed a VAERS report on October 15, 2014, reporting a reaction to A.L.M.'s October 25, 2012 vaccines. Pet. Ex. 12 at 3-4. She reported that A.L.M. suffered a rash on her neck, chest, and face on November 2, 2012. *Id.* In an attached statement, petitioner reported that she called the doctor's office and was told the rash was a normal reaction to immunizations. *Id.* at 4. The rash disappeared within a few hours. *Id.* Within two weeks, A.L.M. started making chewing motions with staring spells, was not reacting to her surroundings, and was motioning as if she was rubbing something between her fingers on her left hand. *Id.* A.L.M.'s physician referred her to neurologist Dr. Dreyer. A.L.M. underwent a 30-minute EEG which was normal. *Id.* Petitioner reported that A.L.M.'s seizures persisted and later included eye twitching. *Id.*

Petitioner took A.L.M. to TCH ER, where she was seen but discharged with a referral to another neurologist. Pet. Ex. 12 at 4. The following day, petitioner took A.L.M. to Memorial Hermann ER, where she was admitted and subsequently transferred to Houston Memorial Hermann Children's Hospital, where staff performed two EEGs, one of which showed seizure activity. An MRI was normal. *Id.* A.L.M. was discharged with a diagnosis of complex partial seizures and prescription for Keppra. *Id.*

A.L.M. then had an appointment with an epilepsy specialist, Dr. Heard, who diagnosed her with complex partial seizure with secondary generalization seizures. Pet. Ex. 12 at 4. Near the end of December 2012, A.L.M. was again admitted to the hospital where doctors switched her to Trileptal. *Id.* According to petitioner, A.L.M.'s seizures were under control with Trileptal, but A.L.M.'s pediatrician and Dr. Heard, as well as petitioner, noticed that A.L.M. was not talking. *Id.* A.L.M.'s speech was evaluated, and she has been in speech therapy, which has improved her speech. *Id.* Petitioner concluded her statement noting that A.L.M. was babbling and saying simple words prior to the seizures; after the seizures began, she was quieter. *Id.*

ii. Additional Records from Pediatrician's Office

Petitioner filed phone logs from the pediatrician's office. Pet. Ex. 4. The record contains a list of telephone calls and office visits between November 26, 2012 and September 18, 2013. Pet. Ex. 4. The record is internally inconsistent and not all entries are contained in the pediatric medical record. Focusing on November and December 2012, Pet. Ex. 4 reflects telephone calls with petitioner on November 2, 2012, December 1, 2012, December 3, 2012, and December 4, 2012. Pet. Ex. 4 at 1-3. However, Pet. Ex. 4 at 3 does not contain the telephone call on December 1, 2012 that is documented at Pet. Ex. 4 at 2. Additionally, Pet. Ex. 4 at 3 includes a telephone call on December 4, 2012 that is not listed on Pet. Ex. 4 at 2. Further, Pet. Ex. 4 at 1 reflects a telephone

call on November 2, 2012, not contained in either Pet. Ex. 4 at 2 or 3. The discrepancies in the record have not been explained.

D. Fact Witness Affidavits and Testimony

i. Affidavit and Testimony of Elizabeth Gram

Petitioner submitted her affidavit with her petition and testified at the hearing. Pet. Ex. 1.

Petitioner testified that A.L.M. was a typical, healthy baby who received all her shots with no problem. Tr. 6-7. On October 25, 2012, she had a one-year-old checkup and received all her vaccinations; no vaccines were declined. Tr. 7.

Petitioner testified that A.L.M. developed a rash on her neck, face, chest, and back on November 2, 2012, one week after her October 25, 2012 vaccines. Tr. 9; *but see* Pet. Ex. 1 at 1, affirming that the rash was on A.L.M.'s chest and face. She telephoned the pediatrician who said it was a normal reaction. Tr. 9. Petitioner stated the rash was gone the next morning. Tr. 10; *but see* Pet. Ex. 12 at 4, stating that the rash disappeared within a few hours. Later during the hearing, petitioner did not remember if the rash was gone within hours or the next day. Tr. 21. Petitioner stated she had to look at the pediatric record for the date of the phone call regarding the rash to know that it was November 2, 2012. Tr. 21. Petitioner felt A.L.M. at the time of the rash and she was not feverish. Tr. 21-22.

Petitioner affirmed "within days and over the next few weeks" A.L.M. began making chewing motions and would sit up abruptly while playing or walking. Pet. Ex. 1 at 2. Petitioner would check her mouth but find nothing. *Id.* Then she began rubbing her fingers together and had eye twitching. *Id.* During these episodes she would stare off, not react to sound or her name, and her eyes would slowly move back and forth. *Id.*

During the hearing, petitioner stated that A.L.M. started chewing and progressed to staring spells, chewing, and rubbing of her fingers within days of the rash. Tr. at 11. The behavior started happening more frequently and progressed to twitching, so petitioner took A.L.M. to the doctor on November 26, 2012. Tr. at 12; Pet. Ex. 1 at 2. The record for that appointment documents that petitioner told the doctor these episodes began a week prior to the November 26, 2012 visit. However, at hearing, petitioner stated the episodes began a few days after the rash and that she "misspoke or misjudged the time frame" because she had a lot going on at the time and her father was terminally ill. Tr. at 13. A.L.M.'s physician referred her to neurologist Dr. Dreyer because her symptoms sounded "like staring spells." Tr. 13.

The week following the appointment, petitioner called the pediatrician to report that A.L.M. had several episodes of "staring, lack of attention to sounds, and trembling." Pet. Ex. 1 at 2. She was told to take A.L.M. to the emergency room. *Id.* While at the TCH ER on December 3, 2012, A.L.M. had an episode. *Id.*

Petitioner affirmed that A.L.M. had episodes throughout the night of December 3, 2012, so petitioner took her to Memorial Hermann Southeast ER. Pet. Ex. 1 at 2. That evening, A.L.M.

was transferred by ambulance to CMHH, where she was admitted for two days. *Id.* The physician ordered an EEG, which showed a seizure. Blood tests were normal. *Id.* A.L.M. was put on Keppra for complex partial seizures; but, according to petitioner, the Keppra was "not working" and "had not helped at all." *Id.* at 3; Tr. 15.

Petitioner affirmed that the episodes increased over the next few weeks and A.L.M.'s whole body would shake, her lips would turn blue, she would not respond to her name, and she would lose bladder/bowel control. Pet. Ex. 1 at 3. Petitioner updated Dr. Grant with the Pediatric Neurology Department at CMHH about what was happening, and he increased A.L.M.'s Keppra dose until she reached the maximum for her age and weight. *Id.* Another neurologist, Dr. Heard, examined A.L.M. later in December 2012, during which time A.L.M. had a seizure; Dr. Heard diagnosed A.L.M. with complex partial seizures and secondary generalization. *Id.*

Petitioner affirmed contacting Dr. Grant on Christmas day to report that A.L.M. was having several seizures a day over shorter timeframes and was on the maximum dose of Keppra. Pet. Ex. 1 at 3. Dr. Grant advised petitioner to take A.L.M. to the ER, have her admitted and her prescription changed. *Id.* During this hospital stay, A.L.M. was weaned off Keppra and switched to Trileptal. *Id.* She was discharged the following day with a diagnosis of temporal lobe seizures. *Id.*

Petitioner affirmed that the Trileptal lessened the frequency of A.L.M.'s seizures. Pet. Ex. 1 at 3. A.L.M. has not had a seizure since February 2013. *Id.*; Tr. at 17. All medication was stopped in late 2015, after A.L.M. had another 24-hour EEG, which came back normal. Tr. at 17-18.

Petitioner stated that A.L.M. was evaluated by speech therapists in October 2013 because her speech and language were not progressing as they should. Pet. Ex. 1 at 4; Tr. 18. At the time of the evaluation, A.L.M. was two years old, but she had the vocabulary of a 15-month-old. *Id.*; Tr. 18. She started speech therapy at age 2. Tr. at 18. Petitioner affirmed A.L.M. has delayed verbal communication and cognitive skills and social interaction issues. Pet. Ex. 1 at 4. At hearing, petitioner stated that A.L.M. still has articulation issues, gets frustrated, and does not handle things emotionally well compared to petitioner's other child. Tr. 18-19. Petitioner considered taking A.L.M. to a child psychologist and back to speech therapy but has not done so yet. Tr. 19-20.

The undersigned questioned petitioner about various items in the VAERS report including petitioner's reports that (1) within hours the rash disappeared, (2) chewing motions started two weeks after the rash, (3) the 24-day gap between the rash on November 2, 2012 and the first doctor's visit on November 26, and (4) the phrase "days to weeks." Tr. 24-30. Petitioner responded that the rash was on A.L.M.'s back, neck, face, and chest until the following morning. Tr. 9, 26-27. After the rash, A.L.M. started with chewing motions, then staring, then hand rubbing, then twitching, and the combination of these symptoms prompted her to take A.L.M. to the doctor on November 26. Tr. 24-26. Her best estimate was that the chewing started within a week or two after the November 2, 2012 rash. Tr. 27. Petitioner then stated that the chewing started within a few days of the rash. Tr. 27. She believed the rash was on a Friday and the chewing, staring off, rubbing fingers, and eye-twitching began within days. Tr. 25-26, 30. Petitioner stated that when she took A.L.M. to the hospital on December 2, 2012 reporting onset of 4 to 6 weeks prior, she was referring to the onset of the rash. Tr. 31. Petitioner confirmed that A.L.M. had no rashes prior to November 2, 2012. Tr. 31. Petitioner agreed she prepared the VAERS report and wrote that the onset of

chewing was approximately two weeks after the rash on November 2, 2012 then things progressed very quickly. Tr. 32-33.

ii. Affidavit and Testimony of Lisa Spencer

Lisa Spencer is petitioner's sister and A.L.M.'s aunt. Tr. 37. She submitted an affidavit and testified at hearing. Pet. Ex. 17; Tr. 36-37. Around the time of her vaccinations, Ms. Spencer saw A.L.M. 3-4 times a week. Tr. 37.

Ms. Spencer affirmed shopping at Target with petitioner and A.L.M. on November 2, 2012 when A.L.M. "broke out in a rash." Pet. Ex. 17 at 1. She stated that petitioner called the doctor and was told that it was a normal post-vaccine reaction but if it got worse, to take A.L.M. to the doctor. *Id.* at 1-2. The rash did not get worse, and they continued shopping. *Id.* at 2.

At hearing, Ms. Spencer was unsure when they were at Target, but it was either on November 7, 8, or 9. Tr. 40. She stated A.L.M. was cranky and had developed a rash on her neck and the front and back of her body. Tr. 38. Petitioner told Ms. Spencer that A.L.M. had her shots a week prior. Tr. 38, 48. Ms. Spencer stated that A.L.M. felt warm at the time. Tr. 39; *but see* Tr. 21-22, where petitioner stated at hearing that A.L.M. was not feverish at the time of the rash. Ms. Spencer stated that petitioner called the doctor who said the rash was normal. Tr. 39.

Ms. Spencer affirmed that petitioner told her A.L.M. had started making chewing motions with nothing in her mouth a few days after the rash. Pet. Ex. 17 at 2. Ms. Spencer then noticed that A.L.M. would stop what she was doing, sit up and make chewing motions. Tr. 40. At the time, she did not think it was something that required medical attention. Pet. Ex. 17 at 2. She then saw A.L.M. rubbing her fingers together, chewing, and staring off into nothing. *Id.* After this started, petitioner took A.L.M. to the doctor. *Id.* Ms. Spencer affirmed that she and petitioner initially thought A.L.M. was just doing "random 'weird' actions all young children occasionally engage in." *Id.* When they all started happening together, they realized medical care was needed. *Id.*

Consistent with her affidavit, Ms. Spencer testified that she noticed a few days after the rash that A.L.M. was making chewing motions and in a little bit of a daze; the week after the rash, she made chewing motions at least once when petitioner dropped A.L.M. off at her house for an hour or two. Tr. 40-41. She didn't think much of it until it progressed where she would sit, stare, chew, and rub her fingers. Tr. 42.

However, on cross examination, Ms. Spencer stated that she witnessed A.L.M. making chewing motions only two days after they were in Target. Tr. 46. She then stated that the family was all together over Thanksgiving, and A.L.M.'s chewing motions had progressed to staring and finger rolling, which led them to take A.L.M. to the emergency room. Tr. 47. Ms. Spencer later corrected herself, saying that this occurred on Christmas day, not Thanksgiving. Tr. 47.

Ms. Spencer testified that she has two children and never saw a rash after their vaccinations, only fussiness and fever, which usually occurred the night of the vaccine or the next day. Tr. 47-48. She never saw a fever from vaccines a week after vaccination. Tr. 48.

According to Ms. Spencer, A.L.M. still has speech issues and writes things backwards, but she is able to understand A.L.M. because her own son has a little stutter. Tr. 43-44.

iii. Affidavit of Sherry Mathison

Sherry Mathison is petitioner's sister who lived with petitioner from August 2012 until January 2013. Pet. Ex. 18 at 1. She submitted an affidavit but did not testify at hearing. *Id.* Ms. Mathison affirmed in August 2012, A.L.M. was a well-behaved, typical child and was speaking a couple of words. *Id.*

Ms. Mathison affirmed in November 2012, A.L.M. began making chewing motions with nothing in her mouth and would rub her hands with nothing in her hand. Pet. Ex. 18 at 2. At first, she and petitioner did not think anything of it. *Id.*

According to Ms. Mathison, "eventually" A.L.M. engaged in all these behaviors at once; she would stop what she was doing, sit down, and make chewing motions while rubbing her fingers together. Pet. Ex. 18 at 2. She further stated that "[i]t was around this time that I also noticed that A.L.M. stopped making an effort to speak the words she learned." *Id.* At this point, petitioner decided to take A.L.M. to the doctor. *Id.*

Ms. Mathison witnessed A.L.M.'s seizures on multiple occasions where A.L.M. would fall to her left side, have body shakes, have her hands at her chest, and her lips would lose color. Pet. Ex. 18 at 2. For an "extended period of time," A.L.M. had several seizures a day and "we could never take our eyes off of her because we never knew when she might have seizure (sic)." *Id.*

V. The Experts' Opinions

A. Qualifications

Petitioner filed four reports from of Dr. Kinsbourne and two reports from Dr. Levin. Pet. Ex. 14, 16, 21, 36, 56[22], 39, 50.

Dr. Marcel Kinsbourne is a medical doctor who specializes in pediatric neurology. Pet. Ex. 57; Tr. 50. He graduated from Oxford University in England in 1955 with a B.M.B.Ch., the equivalent of an American M.D. Pet. Ex. 57 at 2. Dr. Kinsbourne began practicing in the United States as a pediatric neurologist and neuropsychologist in 1967. *Id.* at 3. From 1967 to 2015, Dr. Kinsbourne served as an associate professor in pediatrics and neurology and a senior research associate at Duke University Medical Center before holding a series of academic positions, including professorships in pediatrics, neurology, and psychology. His clinical experience includes serving as a senior staff physician in Ontario from 1974-1980 and a clinical associate in neurology at Massachusetts General Hospital from 1981-1991. *See Fantini v. Sec'y of Health & Human Servs.*, No. 15-1332V, 2022 WL 1760730, at *5 (Fed. Cl. Spec. Mstr. May 2, 2022).

Dr. Kinsbourne's last hospital-based neurology practice was in 1992 and he has since retired from the active practice of neurology. He has had various appointments as a professor since

[22] It appears that Pet. Ex. 16 and 56 are the same report.

with his last position being at the New School in New York, which ended in 2015. Pet. Ex. 57 at 4. An amended CV was filed for Dr. Kinsbourne in this case as Pet. Ex. 57. Dr. Kinsbourne is well known to the Court having been involved in Vaccine Program cases since the inception of the Program, although (as noted in other cases) many years have passed since he has regularly seen patients. *See, e.g.*, *Strong v. Sec'y of Health & Human Servs.*, No. 15-1108V, 2018 WL 1125666, at *6 (Fed. Cl. Spec. Mstr. Jan. 12, 2018); *Pope v. Sec'y of Health & Human Servs.*, No. 14–078V, 2017 WL 2460503, at *8 (Fed. Cl. Spec. Mstr. May 1, 2017).

Dr. Levin graduated from the University of Illinois-Chicago Medical Center in 1964. Pet. Ex. 40. However, he has spent most of the last 25 years since he passed the bar practicing law, with 95% of his income related to his law practice. Tr. 109. He does other work for his wife and Dr. Ramey, the chief epidemiologist from California researching environmentally induced illnesses. Tr. 109-10. He is board certified in allergy, immunology, clinical pathology, and emergency medicine. Tr. 110. Although he spends the majority of his time in the legal field, he keeps his medical board certifications up to date, in part by routinely attending medical lectures. Tr. 110, 126. The last time he taught medicine was 1998, though he has been giving lectures at the VA on environmentally induced illnesses. Tr. 110-11. He still has admitting privileges at UCSF as an attending, but the last time he treated a patient was in 1998. Tr. 111. He last published 20 years ago. Tr. 111-12. Dr. Levin derives about 20% of his income from medical-legal expert work and conceded that his opinions are not popular in the legal system outside of the Vaccine Program. Tr. 112.

Respondent filed four reports from Dr. Holmes and two reports from McCusker. Resp. Ex. A, Q, V, YY, FFF, Z.

Dr. Holmes is a pediatric neurologist. Tr. 128. He earned his medical degree at the University of Virginia, trained in pediatrics at Yale, and returned to the University of Virginia to train in neurology with special competence in pediatric neurology. Tr. 128. He is the chairman of the Department of Neurological Sciences at the University of Vermont. Tr. 128. He spends 50% of his time in clinical practice primarily seeing children with epilepsy. Tr. 128-29. The other 50% of his time is spent doing research, administrative work, and teaching. Tr. 129; Resp. Ex. B.

Dr. McCusker is a pediatric immunologist and allergist. Tr. 184. She has an undergraduate honors degree in microbiology and immunology, a master's degree in molecular virology, and spent three years in a Ph.D. program studying immunology. Tr. 184. She then went to medical school and completed training in allergy, pediatrics, and clinical immunology after medical school. Tr. 184. She later conducted postdoctoral research in an immunology lab for another year. Tr. 184; Resp. Ex. AA.

Dr. McCusker is currently an associate professor of pediatrics at McGill University and the director of the Division of Pediatric, Allergy, Immunology, and Dermatology at the Montreal Children's Hospital and the McGill University Health Center. Tr. 185. She spends 50 percent of her time with patients and doing clinical work and 50 percent of her time in primary research and/or teaching and administration. Tr. 185; Resp. Ex. AA.

B. Causation Opinions

i. The Expert Reports

Dr. Kinsbourne opined that A.L.M.'s growth and development were normal until November 4, 2012, when her seizures began with chewing motions then escalated thereafter. Pet. Ex. 14 at 1-2. At 19- and 23-months of age, A.L.M. knew only a handful of words, required speech therapy and an IEP. *Id.* at 3. A.L.M. has not had a seizure since February 2013. *Id.* at 3. He described the onset of her seizures as "sudden and intense" in the second week following the MMR vaccine. Pet Ex. 14 at 3. He relied on Bourgeois' diagnostic criteria for complex partial seizures of the temporal lobe in infants which includes: (1) predominance of behavioral arrest with possible impairment of consciousness; (2) no identifiable aura; (3) automatisms that are discrete and mostly orofacial; (4) more prominent convulsive activity; and (5) a longer duration (more than 1 minute). *Id.*

Dr. Kinsbourne opined that A.L.M. had a hyperexcitable neural network in the left temporal lobe, seen on the EEG as an active seizure focus in that area of the brain. Pet. Ex. 14 at 4. The localized nature of A.L.M.'s seizure activity was either due to past historical event, such as ischemia or encephalitis, or an underlying structural abnormality. *Id.* The focal origin featured abnormal connectivity between neurons, making it more likely to discharge and cause a lowered seizure threshold. Pet. Ex. 14 at 4-5; Pet. Ex. 32.[23] He explained that the propensity for seizure activity is greater in infancy because inhibitory GABA interneurons that present later in life are premature in infancy. Pet. Ex. 14 at 4; Pet. Ex. 27.[24] These interneurons act as an excitatory neurotransmitter, potentially feeding incipient paroxysmal discharge. *Id.* Dr. Kinsbourne referred to focal cortical dysplasia as an example of a neural disorder that lowers seizure threshold. Its' neural mechanisms "apply broadly to other epileptogenic structural anomalies of cortical neural networks," and greater than 24% of epilepsies are associated with cortical malformations. *Id.* at 5. Genetic causes or vascular malformations, stroke, and posttraumatic scars were all ruled out in A.L.M.'s case by an MRI and genetic testing; thus, cerebral cortical dysgenesis being the largest diagnostic category supports his view that it is medically reasonable A.L.M.'s vaccination more likely than not triggered her complex partial seizure disorder. *Id.*

However, Dr. Kinsbourne explained, cortical dysplasia alone would not be sufficient to trigger epilepsy. Pet. Ex. 14 at 5, 6. He described a two-hit theory whereby a latent brain abnormality exists which is then provoked by a second hit—here, the MMR vaccine. *Id.* at 6. Regarding the first hit, areas of cortical dysgenesis feature microglial activation which releases proinflammatory cytokines, including interleukin-1 beta (also referred to a "IL-1beta", "IL-1b", or "IL-1β"), imposing on an already lowered seizure threshold. *Id.* at 7.[25] Vaccinations serve as the second hit, activating the innate immune system to release proinflammatory cytokines including

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[23] David A. McCormick & Diego Contreras, *On the Cellular and Network Bases of Epileptic Seizures*, 63 ANN. REV. PHYSIOLOGY 815 (2001), filed as "Pet. Ex. 32."

[24] Ilgam Khalilov et al., *Epileptogenic Actions of GABA and Fast Oscillations in the Developing Hippocampus*, 48 NEURON 787 (2005), filed as "Pet. Ex. 27."

[25] Jieun Choi & Sookyong Koh, *Role of Brain Inflammation in Epileptogenesis*, 49 YONSEI MED. J. 1 (2008), filed as "Resp. Ex. J."

IL-1b, which is necessary for the stimulation of an adaptive response to confer immunity.[26] *Id.* at 6. IL-1b specifically has a "well-documented propensity to cause seizures, and seizure activity tends to cause further release" IL-1b. *Id.*; Pet. Ex. 34.[27] The receptor for IL-1b is expressed by neurons in the hippocampus and other seizure-sensitive regions of the brain. Pet. Ex. 14 at 6-7. When IL-1b binds to its receptor, it causes enhanced neuronal excitability and a decreased seizure threshold. *Id.* at 7. The second hit would initiate the cycle of seizure begetting seizure, thus leading to epilepsy. *Id.* at 6.

Dr. Kinsbourne posited that patients with congenital/perinatal dysplastic lesions do not express epilepsy until later in life and if they do, it is after some trigger. Pet. Ex. 14 at 6. The stressors, or second hit, may facilitate eventual epileptogenesis. *Id.* Epileptogenic focus located in the left temporal lobe results in delays in "language comprehension skills and persisting deficits in speech expression." *Id.*

Succinctly, Dr. Kinsbourne's theory presumes the existence of a hyperexcitable neural network or lower-than-normal seizure threshold due to congenital or perinatal lesions on the brain as the first hit. Pet. Ex. 14 at 7. The MMR, which released IL-1b necessary to stimulate an adaptive immune response, triggered the hyperexcitable neural network in the temporal lobe, causing seizure onset emanating from that area of the brain as the second hit. *Id.* Dr. Kinsbourne also opined that A.L.M.'s seizures occurred in a medically reasonable time after her MMR vaccination. *Id.* He further stated that there was no evidence of an alternative cause. *Id.*

Dr. Holmes issued a responsive report in which he opined that A.L.M.'s clinical course was consistent with idiopathic epilepsy, and her language dysfunction was indicative of the location from where her seizures arose. Resp. Ex. A at 6. He noted that the cause of epilepsy is unknown in approximately 55-75% of cases. *Id.* at 7.

Dr. Holmes agreed that vaccines are intended to activate the innate immune system and cause the release of proinflammatory cytokines. Resp. Ex. A at 7. He disagreed that there is any evidence that the MMR vaccine can cause an inflammatory reaction in the temporal lobe that results in seizures and language delay. *Id.* Dr. Holmes added that A.L.M. had no symptoms of inflammatory reactions after her vaccinations only a transient rash. *Id.* Further, she does not have cortical dysgenesis. Clinically, her EEG and MRI showed no acute inflammatory response and none of her treaters considered her epilepsy to be vaccine related. *Id.* Further, the Institute of Medicine ("IOM") concluded that an association between the MMR vaccine and afebrile seizures is lacking. *Id.* Dr. Holmes posited that "there is no evidence to indicate the MMR vaccine results

[26] Akiko Iwasaki & Ruslan Medzhitov, *Toll-like Receptor Control of the Adaptive Immune Response*, 5 NATURE IMMUNOLOGY 987 (2004). This article was not filed.

[27] Annamaria Vezzani, PhD & Tallie Z. Baram, MD, PhD, *New Roles for Interleukin-1 Beta in the Mechanisms of Epilepsy*, 7 EPILEPSY CURRENTS 45 (2007), filed as "Pet. Ex. 34."

in non-febrile seizures. *Id.*; Resp. Ex. M;[28] Resp. Ex. N;[29] Resp. Ex. O.[30] In conclusion, Dr. Holmes believed that A.L.M. has "well controlled epilepsy and an expressive speech disorder." Resp. Ex. A at 8.

Dr. Kinsbourne responded to Dr. Holmes' report, clarifying that his reference to cortical dysgenesis in his first report was for illustrative purposes only. Pet. Ex. 16 at 1. He agreed that A.L.M. does not have cortical dysgenesis. *Id.* He argued that his theory, which involves the release of proinflammatory cytokines, specifically IL-1b, is a medically reasonable mechanism to show that vaccines can cause or trigger the onset of seizures to satisfy Prong I. *Id.* at 2. It is well known that vaccines produce proinflammatory cytokines necessary to achieve immunity. *Id.* Dr. Kinsbourne submitted that only the MMR vaccination A.L.M. received could cause seizures in the second week after vaccination, agreeing that the timeframe was not as plausible for the other vaccines. *Id.*

Dr. Kinsbourne issued a third report addressing afebrile seizures and MMR vaccine, asserting that seizures may occur without fever. Pet. Ex. 21 at 1, 5; Pet. Ex. 29;[31] Pet. Ex. 35.[32] According to Dr. Kinsbourne, while "IL-1beta also causes fever…the epileptogenic effect of IL-beta is not mediated by its propensity also to elevate body temperature." *Id.* at 5; Pet. Ex. 24.[33] Dr. Kinsbourne explained that IL-1beta is expressed in neurons in the hippocampus and other seizure-sensitive areas of the brain and when it binds to its receptor, it causes enhanced neuronal excitability and decreased seizure threshold. Pet. Ex. 21 at 5. The presumption that A.L.M. had a lowered seizure threshold is required and is reasonable "since great numbers of other children who receive [the MMR vaccine] do not have seizures." *Id.*

Further, Dr. Kinsbourne submitted, "here, seizures occurred after MMR vaccination and during the period of viremia from the attenuated live measles virus. As with mild infections, a minority of seizures are afebrile. A substantial amount of literature documents afebrile seizures occurring in the risk period after MMR vaccination." Pet. Ex. 21 at 5. For example, *Le Saux* reported 78 cases of new onset seizures, of which 16 were afebrile; further, there were "33 reports of hospitalization for afebrile seizures occurring 5 to 30 days after receipt of MMR vaccine." Pet. Ex. 21 at 5; Pet. Ex. 31.[34] Further, *von Spiczak* reported 44 cases of afebrile seizures, as compared

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[28] Robert L. Davis & William Barlow, *Placing the Risk of Seizures with Pediatric Vaccines in a Clinical Context*, 5 PEDIATRIC DRUGS 717 (2003), filed as "Resp. Ex. M."

[29] William E. Barlow, PhD et al., *The Risk of Seizures After Receipt of Whole-cell Pertussis or Measles, Mumps, and Rubella Vaccine*, 345 NEW ENGLAND J. OF MEDICINE 656 (2001), filed as "Resp. Ex. N."

[30] V. Demicheli et al., *Vaccines for Measles, Mumps, and Rubella in Children (Review)*, COCHRANE DATABASE SYST REV. (2012), filed as "Resp. Ex. O."

[31] Lee & Ong, *supra* note 5.

[32] Ting Zhang et al., *Are Afebrile Seizures Associated with Minor Infections a Single Seizure Category? A Hospital-based Prospective Cohort Study on Outcomes of First Afebrile Seizure in Early Childhood*, 55 EPILEPSIA 1001 (2014), filed as "Pet. Ex. 35."

[33] Céline M. Dubé et al., *Febrile Seizures: Mechanisms and Relationship to Epilepsy*, 31 BRAIN AND DEVELOPMENT 366 (2010), filed as "Pet. Ex. 24."

[34] Nicole Le Saux, MD, et al., *Decrease in Hospital Admissions for Febrile Seizures and Reports of Hypotonic-hyporesponsive Episodes Presenting to Hospital Emergency Departments Since Switching to Acellular Pertussis Vaccine in Canada: a Report from IMPACT*, 112 PEDIATRICS 348, 351 (2003), filed as "Pet Ex. 31."

with 136 cases of febrile seizures, noting "[s]ingle afebrile seizures were reported in 44 (17.8%) of 247 cases, including single focal seizures (n = 4), tonic seizures (n = 2), atonic seizures (n = 3), generalized tonic-clonic seizures (n = 14), and afebrile status epilepticus (n = 6)." Pet. Ex. 21 at 5; Pet. Ex. 33.[35]

Dr. Kinsbourne agreed that the IOM committee on adverse effects of vaccines by *Stratton*[36] did not credit any of the "numerous reports of afebrile seizures related to MMR." Pet. Ex. 21 at 5. However, he claimed the committee "hardly credits any causal relations between any vaccine and any adverse event, since it chose a standard of adjudication that is quite unrealistically elevated for purposes of vaccine injury compensation proceedings." *Id.*

In his second report, Dr. Holmes agreed that A.L.M. had localized epilepsy emanating from the left hemisphere of her brain. Resp. Ex. Q at 2. He agreed that seizures arise from abnormal brain tissue. *Id.* However, Dr. Holmes was unclear about petitioner's two-hit theory, specifically, what constituted the first hit and what the biological mechanism was for the MMR to be the second hit. *Id.* He pointed out that there is no evidence that A.L.M. had any inflammatory response following her vaccines. *Id.*

Dr. Holmes added that "the adjusted incidence of new-onset epilepsy in children is 44.5 cases per 100,000 persons per year with the highest incidence rates in the first year of life." Resp. Ex. Q at 3. Neither the *Le Saux* nor the *von Spiczak* studies relied on by Dr. Kinsbourne examined the comparative risk of afebrile seizures in children who were not immunized. *Id.*; Pet. Ex. 31;[37] Pet. Ex. 33.[38] Dr. Holmes agreed that a small number of children have developed epilepsy after having afebrile seizures following an MMR vaccine but submitted those children would have likely developed epilepsy regardless. Resp. Ex. Q at 3. For this reason, neither *Le Saux* nor *von Spiczak* were considered by the IOM in evaluating epidemiologic or mechanistic evidence related to the MMR vaccine; the IOM ultimately concluded that an association between MMR and afebrile seizures was lacking. *Id.*; Pet. Ex. 31;[39] Pet. Ex. 33.[40] Additionally, Dr. Holmes added, the *von Spiczak* article specifically noted that "passive surveillance [is] not suitable for determining the frequency of a particular adverse effect." Resp. Ex. Q at 3; Pet. Ex. 33.[41] In sum, Dr. Holmes restated his opinion that A.L.M. has well controlled epilepsy and an expressive language disorder, but disagreed her neurological condition was related to the vaccine. Resp. Ex. Q at 3.

In his fourth report and in response to questions raised by the undersigned, Dr. Kinsbourne submitted that the exact abnormality on the brain is immaterial; what matters is that abnormal brain tissue exists in the area from which the epilepsy is generated. Pet. Ex. 36 at 1. Dr. Kinsbourne added, "[t]he evidence that A.L.M. had a lowered seizure threshold resides in the facts of this case." *Id.* All that is necessary is that the person's brain tissue includes hyperexcitable neuronal

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[35] Sarah von Spiczak et al., *A Retrospective Population-based Study on Seizures Related to Childhood Vaccination*, 52 EPILEPSIA 1506 (2011), filed as "Pet. Ex. 33."
[36] Based on review of the record, it does not appear that the Stratton et al. (2012) article was filed.
[37] Le Saux et al., *supra* note 34.
[38] von Spiczak et al., *supra* note 35.
[39] Le Saux et al., *supra* note 34.
[40] von Spiczak et al., *supra* note 35.
[41] *Id.*

tissue, by virtue of which the seizure threshold is lowered; this renders the individual susceptible to generating seizures if provoked by a triggering event, such as receiving a vaccine. *Id.* According to Dr. Kinsbourne, "[t]he damage to the neural network could theoretically have been inflicted by the vaccinations. But far more likely it was in place before the vaccination, which rendered this susceptibility into the reality of [A.L.M.'s] seizure disorder." *Id.*

Dr. Kinsbourne claimed that the *Dubé* and *Vezzani* articles support his opinion that proinflammatory cytokines—IL-1b—can cause seizures as well as fever, though one is not contingent on the other. Pet. Ex. 36 at 2; Pet. Ex. 38; [42] Pet. Ex. 37. [43] He further opined that a seizure triggered by measles viremia need not be accompanied by fever. Pet. Ex. 36 at 2. Pointing to a chart contained in the *Vezzani* study, Dr. Kinsbourne suggested that IL-beta generates epileptogenesis through different pathways that can be activated in parallel, but neither of which features fever. *Id.*; Pet. Ex. 37.[44]

Dr. Kinsbourne conceded whether she had fever or no fever and regardless of if her seizure threshold was lowered or her neural network hyperexcitable, the vaccine would not be responsible for A.L.M.'s seizures if it is found that her seizures had an onset in excess of two weeks after the MMR vaccine. Pet. Ex. 36 at 2.

Dr. Holmes responded in a third report, which addressed the temporal relationship between vaccination and symptom onset. He submitted that febrile seizures present between 7-14 days after MMR vaccination but can range from hours to 28 days. Resp. Ex. V at 2. If the time interval between A.L.M.'s MMR vaccine and her first seizure is found to be 31 days, then it would fall outside of the timeframe even for MMR-induced febrile seizures. *Id.* However, Dr. Holmes posited there is no biological mechanism by which the MMR vaccine can cause afebrile seizures. *Id.* Further, neither *Dubé* nor *Vezzani* address vaccination-induced proinflammatory cytokines. *Id.* at 3; *See* Pet. Ex. 38;[45] Pet. Ex. 37.[46] He added neither *Dubé* nor Dr. Kinsbourne have explained how the MMR vaccine can increase cytokines in the absence of fever and cause seizures. Resp. Ex. V at 3.

Dr. Holmes further opined that there was no evidence either epidemiologically or mechanistically to support Dr. Kinsbourne's opinion that A.L.M. had "hyperexcitable neuronal tissue," resulting in a lower seizure threshold and rendering her susceptible to a seizure disorder that was activated by the MMR vaccine. Resp. Ex. V at 2-3.

Petitioner's expert Dr. Levin issued a report which also discussed the two-hit theory. Pet. Ex. 39 at 2. Dr. Levin proposed that the first hit was from birth trauma or a genetic propensity that

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[42] Céline M. Dubé et al., *Cytokines: A Link Between Fever and Seizures: Interleukin-1b Contributes to the Generation of Experimental Febrile Seizures*, 57 ANN. NEUROLOGY 152 (2005), filed as "Pet. Ex. 38" and "Resp. Ex. QQ."

[43] Annamaria Vezzani et al., *The Role of Cytokines in the Pathophysiology of Epilepsy*, 22 BRAIN, BEHAVIOR, & IMMUNITY 797 (2008), filed as "Pet. Ex. 37."

[44] *Id.* at 801.

[45] Dubé et al., *supra* note 42.

[46] Vezzani et al., *supra* note 43.

lowered seizure threshold. *Id.* The second hit was from "the multiple vaccinations"[47] A.L.M. received on October 25, 2012 that caused or substantially contributed to her seizures and epilepsy, with or without fever, because "all vaccines are engineered to activate the innate immune system and cytokine enhancement." *Id.* at 1-2. The enhanced cytokine production, then caused neuronal damage. Pet. Ex. 39 at 2. The first clinical signs of neuronal damage were the chewing motions, staring, not reacting to sound, and rubbing of her fingers, all of which began within two weeks of the vaccination. *Id.* The seizures "were simply a further indication of the progression of neuronal damage and were noted one month later."[48] *Id.* A.L.M.'s rash on November 2 was an inflammatory response caused by cytokine production evoked by vaccination. *Id.*

Dr. Levin opined that MMR vaccine is associated with afebrile seizures relying on *Eckerle*, *Weibel*, and the MMR vaccine package insert. Pet. Ex. 39 at 2; Pet. Ex. 41;[49] Pet. Ex. 45;[50] Pet. Ex. 43. According to Dr. Levin, peripheral vaccinations produce cytokines, which can cause both fevers and seizures independent of one another, writing, "seizures are caused by the neuronal damage which, in turn, is caused by the cytokines and independent of the fever." Pet. Ex. 39 at 2; Pet. Ex. 42.[51]

Dr. Levin concluded that Prong I was "clearly" established in "[t]he fact that her symptoms began within 2 weeks of the vaccination and they **all** biologically plausibly related to cytokine reactions satisfies the 1st first signs of cytokine induced neuronal damage is totally appropriate satisfies the 2nd prong."[52] Pet. Ex. 39 at 2 (emphasis in original). Further, Dr. Levin opined that the vaccinations received by A.L.M. on October 25, 2012 were the cause or substantial contributor to her neurologic pathology. *Id.*

Dr. McCusker responded to both Drs. Kinsbourne and Levin in her first report. She provided an in-depth explanation of how vaccines work to produce immunity and the function of cytokines. Resp. Ex. Z. She defined cytokines as communication proteins that interact with receptors, inducing a response that affects the behavior and the function of the recipient cell. *Id.* at 3. "Cytokines shape the innate and adaptive immune response and depending upon the profile and amount of cytokines released these responses may be pro- or anti-inflammatory." *Id.* Unlike cytokines expressed in the periphery, cytokines expressed in the brain can play a distinct role in normal brain homeostasis and are not considered "pro inflammatory." *Id.* at 3-4.

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[47] Notably, Dr. Levin agreed with Dr. Kinsbourne that the MMR vaccine was the "lead actor[] in this scenario, however the contribution of the other eighteen pathogen simulating antigens, DTaP, Hib, Prevnar 13 and Varicella . . . should not be ignored in this baby's neuropathology." Pet. Ex. 39 at 1.

[48] It appears that Dr. Levin placed seizure onset approximately one month after A.L.M.'s vaccination, which is consistent with petitioner's VAERS report and with the medical records. However, this is inconsistent with Dr. Kinsbourne's proposed date of seizure onset, which was roughly ten days following A.L.M.'s vaccination. *See* Tr. 54. This issue will be discussed further in Prong III.

[49] Isabella Eckerle et al., *Nonfebrile Seizures after Mumps, Measles, Rubella, and Varicella-Zoster Virus Combination Vaccination with Detection of Measles Virus RNA in Serum, Throat, and Urine*, 20 CLINICAL & VACCINE IMMUNOLOGY 1094 (2013), filed as "Pet. Ex. 41."

[50] Robert E. Weibel, MD et al., *Acute Encephalopathy Followed by Permanent Brain Injury or Death Associated with Further Attenuated Measles Vaccines: A Review of Claims Submitted to the National Vaccine Injury Compensation Program*, 101 PEDIATRICS 383 (1998), filed as "Pet. Ex. 45."

[51] Ichiyama et al., *supra* note 15.

[52] This is a direct quote, and it is unclear what this means.

Dr. McCusker submitted that fever, for example, is the effect of cytokines such as IL1b, IL6 and Tumor Necrosis Factor Alpha ("TNFα"). *Id.* at 3. These cytokines are part of the initial cascade of inflammation at the site of infection or trauma which is usually transient and tightly regulated. Resp. Ex. Z at 3. Most cytokine events occur locally and do not generate significant systemic signaling. *Id.* Even with live viruses, the zone of activity is primarily limited to the local lymph nodes. *Id.* at 8. Further, there is no evidence that cytokines produced from a peripheral vaccination can trigger epilepsy generally or that it did here. *Id.*

Dr. McCusker relied on *Kashiwagi*, to explain cytokine upregulation following receipt of vaccines that is transient and tightly regulated. Resp. Ex. Z at 5; Resp. Ex. GG.[53] Notably, examination of serum cytokine levels in children within 48 hours of vaccination showed very low amounts of IL-1b, IL6, and TNFα, suggesting that the level of cytokines produced and released by the peripheral immune system during vaccination is not sufficient to influence the development of cytokine-mediated changes in seizure threshold as proposed by petitioner's experts. Resp. Ex. Z at 5. She acknowledged that *Kashiwagi* did not study live viral vaccinations like the MMR vaccine, but did study Hib, DPT, and 7-valent pneumococcal vaccines; however, studies of wild type measles infection did not show high levels of IL-1b. *Id.*; Resp. Ex. GG.[54]

Dr. McCusker referenced *Dubé* to show that the cytokine levels after peripheral vaccination showed no evidence of significant cytokine changes in the brain. Resp. Ex. Z at 7. In *Dubé*, large amounts of IL-1beta were injected directly into the brains of mice. The level of cytokines necessary to induce a lowered seizure threshold in the mice was more than 1000 times greater than that found in the blood during actual measles infection. *Id.* Dr. McCusker estimated that IL-1b levels after an attenuated strain vaccine, like MMR vaccine, would be similar to or less than the levels seen in wild type measles infection. *Id.* at 5. Thus, even if peripheral IL-1b was detectable when A.L.M. had the rash on November 2, 2012, the level would have been low. *Id.* Further, she claimed that there is no evidence of sustained IL-1b in this case. *Id.*

Dr. McCusker referenced the *Ron-Harel* and *Moidunny* studies to show that cytokines play a role in normal brain function due to their function in neuroprotection and neuromodulation. Resp. Ex. Z at 5; Resp. Ex. II;[55] Resp. Ex. JJ.[56] At baseline, microglial cells present in the brain release cytokines and can increase from stressors but are involved in basic brain physiology. Resp. Ex. Z at 5. The *Li* study showed that cytokines may even reduce the risk of seizure activity, concluding that "IL-1beta, in the CNS in general, reduces rather than augments neuronal activity." Resp. Ex.

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[53] Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type b (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 HUMAN VACCINES & IMMUNOTHERAPEUTICS 677 (2014), filed as "Resp. Ex. GG."

[54] *Id.*

[55] Noga Ron-Harel et al., *Brain Homeostasis is Maintained by ''Danger'' Signals Stimulating a Supportive Immune Response Within the Brain's Borders*, 25 BRAIN, BEHAVIOR, & IMMUNITY 1036 (2011), filed as "Resp. Ex. II."

[56] Shamsudheen Moidunny et al., *Interleukin-6-type Cytokines in Neuroprotection and Neuromodulation: Oncostatin M, but Not Leukemia Inhibitory Factor, Requires Neuronal Adenosine A_1 Receptor Function*, 114 J. OF NEUROCHEMISTRY 1667 (2010), filed as "Resp. Ex. JJ."

Z at 7; Resp. Ex. RR.[57] She added that *Vezzani & Baram*, who chemically induced seizures with large amounts of IL-1b injected directly into the hippocampus of rats, found that IL-1b administered peripherally had an anticonvulsant effect. Resp. Ex. Z at 8; Pet. Ex. 34.[58] While cytokines from the periphery can cross the blood brain barrier and stimulate nerve fibers in areas of inflammation, causing upregulation in the various areas of the brain leading to sickness behavior such as fever there is no evidence that low concentrations of peripheral cytokines result in significant increases or overexpression of these cytokines in the brain tissue. *Id.* at 7.

Dr. McCusker posited that cytokines in the brain are produced in response to and serve as the etiology for seizures not the cause of seizures as opined by Drs. Kinsbourne and Levin. Resp. Ex. Z at 7, 8. There is no evidence to show that the peripheral release of IL-1b or other pro-inflammatory cytokines following vaccination can cause epilepsy. *Id.* at 8. Dr. McCusker pointed out that *von Spiczak* concluded, "the risk for epilepsies is not elevated even though epilepsy may present with a seizure following vaccination." Resp. Ex. Z at 8; Pet. Ex. 33.[59] The authors further stated that "[c]arefully designed studies have failed to demonstrate an association between vaccination and adverse neurological outcome in children." Resp. Ex. Z at 8, Pet. Ex. 33.[60] Further, the authors in *Verbeek* concluded that the results supported their hypothesis that predisposing factors within the child—and not the vaccination—caused the observed neurologic deterioration. *Id.*; Resp. Ex. UU.[61]

Dr. McCusker added that epidemiological studies demonstrate that the incidence of epilepsy is highest in infancy and seizure onset in the first year of life most commonly occurs before the age of 7 months. Resp. Ex. Z at 8. She also noted that onset of focal epilepsy is mainly in infancy. *Id.* at 7; Resp. Ex. PP.[62] Further, more than 60% of those patients with epilepsy show no neurological deficits at the time of onset and 37% have normal MRIs. Resp. Ex. Z at 7; Resp. Ex. PP.[63] Although there is a temporal association between seizures and vaccination, the events have yet to be etiologically linked. Resp. Ex. Z at 8-9.

Dr. McCusker noted that A.L.M. had many events since birth that activated peripheral immunity by releasing cytokines, including an RSV infection at 5 weeks of age, vaccinations at 2, 4, 6 and 12 months of age, and gastroenteritis during the summer of 2012. Resp. Ex. Z at 4. At 12 months old, she received multiple vaccinations and experienced no fever, no evidence of inflammation at the vaccination site reported and no sick behaviors. *Id.* at 5. After her subject vaccinations, there were no symptoms of systemic cytokine activation, although she did have a rash on November 2, 2012. *Id.*; *see also* Resp. Ex. EE.[64]

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[57] Gang Li et al., *Cytokines and Epilepsy*, 20 SEIZURE 249 (2011), filed as "Resp. Ex. RR."
[58] Vezzani & Baram, *supra* note 27.
[59] von Spiczak et al., *supra* note 35.
[60] *Id.* at 8.
[61] Verbeek et al., *Etiologies for Seizures Around the Time of Vaccination*, 134 PEDIATRICS 658 (2014), filed as "Resp. Ex. UU."
[62] Marilena Vecchi, *Symptomatic and Presumed Symptomatic Focal Epilepsies in Childhood: An Observational, Prospective Multicentre Study*, 57 EPILEPSIA 1808 (2016), filed as "Resp. Ex. PP."
[63] *Id.*
[64] Maria I. Oliveira et al., *Rash After Measles Vaccination: Laboratory Analysis of Cases Reported in São Paulo, Brazil*, 36 REVISTA DE SAUDE PUBLICA 155 (2002), filed as "Resp. Ex. EE."

Dr. McCusker opined that A.L.M. had a seizure disorder which manifested weeks after her vaccination. Resp. Ex. Z at 9. Though the precise timing of onset was unclear, there is no evidence in the medical records or medical literature to support the idea that A.L.M.'s vaccinations led to her seizure disorder. *Id.* Studies show that IL-1b levels after vaccination are very low and only small amounts are detected in patients even with wild-type measles infection when they manifest with rash. *Id.* The levels required to decrease seizure threshold would be even greater than what is detected in patients who have severe symptoms requiring hospitalization due to natural infection. *Id.* Therefore, there is no evidence of a causal link between A.L.M.'s vaccination and her seizures. *Id.*

Dr. Levin responded, maintaining his opinion that twenty-one separate infectious antigens and adjuvants received caused an inflammatory response, with A.L.M.'s rash on November 2 as consistent with a cytokine-induced inflammatory cutaneous reaction. Pet. Ex. 50 at 1.

Further, Dr. Levin maintained that fever and seizures are independent of one another. Pet. Ex. 50 at 1. He relied on *Dubé* admitting that when recombinant IL-1b was administered to wild type mice it decreased seizures but at high doses was sufficient to induce seizures in afebrile animals. *Id.*; Pet. Ex. 38.[65] *Vezzani* showed that afebrile seizures themselves led to the expression of IL-1b in microglia, claiming that IL-1b induced by seizures may in turn exacerbate ongoing seizures acting as its neuronal receptor. Pet. Ex. 50 at 1; Pet. Ex. 55.[66] He submitted that seizures are caused by the lowering of seizure thresholds in neurons and from edema. Pet. Ex. 50 at 2; Pet. Ex. 52.[67] He concluded that fever and seizures are caused by independent pathways with fever caused by the interaction of endogenous and exogenous cytokines on the hypothalamus and other portions of the brain. Pet. Ex. 50 at 2; Pet. Ex. 53.[68]

Dr. Levin criticized the literature relied on by Dr. McCusker referring to *Kashiwagi* and *Lin* as "irrelevant" and "inaccurate". Pet. Ex. 50 at 2-3; *See* Resp. Ex. GG,[69] Resp. Ex. HH.[70] He submitted that Dr. McCusker offered *Kashiwagi* to show that the cytokines released by vaccines are very low; but her interpretation was "inaccurate and unrelated to" *Dubé*. Pet. Ex. 50 at 2. According to Dr. Levin, *Dubé* [71] identified changes in brain cells after the direct injection of

[65] Dubé et al., *supra* note 42.
[66] Annamaria Vezzani et al., *Interleukin-1b Immunoreactivity and Microglia Are Enhanced in the Rat Hippocampus by Focal Kainate Application: Functional Evidence for Enhancement of Electrographic Seizures*, 19 J. OF NEUROSCIENCE 5054 (1999), filed as "Pet. Ex. 55."
[67] Einar E. Eriksson et al., *Direct Observations In Vivo on the Role of Endothelial Selectins and Alpha (4) Integrin in Cytokine-induced Leukocyte-endothelium Interactions in the Mouse Aorta*, 86 CIRCULATION RES. 526 (2000), filed as "Pet. Ex. 52."
[68] Mihai G. Netea et al., *Circulating Cytokines as Mediators of Fever*, 31 CLINICAL INFECTIOUS DISEASES 178 (2000), filed as "Pet. Ex. 53." This article discusses fever as an important part of the body's response to exogenous factors and the many ways and through various organs that the body can generate fever.
[69] Kashiwagi et al., *supra* note 53.
[70] Wen-Hsuan W. Lin et al., *Plasma Cytokines and Chemokines in Zambian Children with Measles: Innate Responses and Association With HIV-1 Coinfection and In-Hospital Mortality*, 215 J. OF INFECTIOUS DISEASES 830 (2017), filed as "Resp. Ex. HH."
[71] Dubé et al., *supra* note 42.

cytokines into the brain; *Kashiwagi*,[72] on the other hand, studied peripheral blood cells, not brain cells. *Id.* at 2-3. Further, *Lin*[73] studied acute viral diseases not vaccinations. *Id.* at 3. Dr. Levin concluded that *Dubé*[74] "clearly" shows that cytokines cause seizures and fevers separately, supporting his theory that vaccine(s) can cause an afebrile seizure. *Id.*

Dr. Holmes issued a report in response to Dr. Levin. Resp. Ex. YY at 2. He posited that there was no birth trauma in this case, citing to A.L.M.'s Apgar scores, her newborn screening, and her numerous well-child visits. *Id.* Dr. Holmes also stated he was unclear on what Dr. Levin was referring to as the "first hit." *Id.*

Dr. Holmes agreed that the MMR vaccine elicits an innate response, but there was no proof that A.L.M.'s innate immune response resulted in a neurological injury as Dr. Levin suggested. Resp. Ex. YY at 3. Dr. Holmes explained that within hours of the introduction of an antigen to the body, an innate immune response occurs, wherein B and T cells are activated by macrophages and dendritic cells that engulf the antigen. *Id.* These new antigen-presenting cells present the antigen to T cells and then release inflammatory cytokines and chemokines that recruit, activate, and proliferate the B and T cells. *Id.* Then, activated B and T cells "release inflammatory mediators leading to the recruitment and activation of additional immune cells that further amplify the immune response through the release of inflammatory mediators." *Id.* There is no evidence in this case that the MMR vaccine A.L.M. received resulted in her suffering from a systemic response that caused brain damage. *Id.* Dr. Levin provided no support for his argument other than relying on a transient rash. *Id.*

Dr. Holmes explained that children develop rashes all the time for various reasons and some following MMR immunization. Petitioner affirmed that A.L.M.'s rash appeared a week after her vaccinations and lasted less than an hour. Resp. Ex. YY at 3. A.L.M.'s EEG showed no acute inflammatory brain injury. *Id.* According to Dr. Holmes, Dr. Levin's opinion—that the MMR vaccine led to "an intense release of cytokines that resulted in a transient rash and elicited brain damage in a child who had no signs or symptoms of central nervous system disease" leading to permanent brain injury—is "implausible from both a clinical and biological standpoint." *Id.*

Dr. Holmes discussed the *Weibel* and *Eckerle* studies relied on by Dr. Levin in support of his theory that MMR vaccine can cause afebrile seizures. Resp. Ex. YY at 4; Pet. Ex. 41;[75] Pet. Ex. 45.[76] Dr. Holmes submitted that *Weibel* was based on passive retrospective surveillance with no control group and discussed children who developed encephalopathy of no determined cause within 15 days of MMR; the authors found a clustering with peak onset of cases on days 8 and 9 after immunization. Resp. Ex. YY at 4; Pet. Ex. 45.[77] Here, however, A.L.M. did not develop encephalopathy 8 or 9 days after vaccination. Resp. Ex. YY at 4. Further, *Eckerle* is a case study of one child who had three generalized tonic clonic seizures 6 days after MMR/varicella vaccines.

[72] Kashiwagi et al., *supra* note 53.
[73] Lin et al., *supra* note 70.
[74] Dubé et al., *supra* note 42.
[75] Eckerle et al., *supra* note 49.
[76] Weibel et al., *supra* note 50.
[77] *Id.*

Resp. Ex. YY at 4; Pet. Ex. 41.[78] The authors concluded that it was not possible to assess a causal relationship between afebrile seizures and vaccination. Resp. Ex. YY at 4.

Dr. Holmes disagreed that A.L.M.'s neuropathology was neuronal damage caused by cytokines enhanced by the vaccination on October 25, 2012. Resp. Ex. YY at 4. There was no proof in the record of neuronal damage, and Dr. Levin failed to explain what he was referring to as "obvious signs" of neuronal damage. *Id.* Notably, none of A.L.M.'s treaters recognized obvious signs of neuronal damage either. *Id.*

Dr. Holmes further took issue with Dr. Levin's opinion that cytokines produced from peripheral vaccinations can cause fever and seizures independent of one another. Resp. Ex. YY at 4. He discussed the *Ichiyama* study relied on by Dr. Levin, noting that the study was of prolonged febrile seizures in children with acute encephalitis/encephalopathy associated with fever. The study did not involve vaccines at all. *Id.*; Pet. Ex. 42.[79] Further, A.L.M. did not have febrile seizures or encephalopathy. Resp. Ex. YY at 4. Dr. Holmes concluded that Dr. Levin's opinion lacked any support from the medical record or credible literature. *Id.*

Dr. McCusker issued a report in response to Dr. Levin, addressing A.L.M.'s rash. She explained that the rash that develops 7-10 days after the MMR vaccination marks the body's clearance of the infectious virus and the end of inflammation. Resp Ex. FFF at 3; Resp. Ex. GGG.[80] Evidence shows that following the resolution of the rash, the dominant active immune response is regulatory, anti-inflammatory T cells. *Id.* Thus, inflammatory cytokines would not circulate after the rash. *Id.* Here, if A.L.M.'s rash was vaccine related, it was an indication that the inflammation process had ended. *Id.*

Dr. McCusker also explained the concept of cytokine half-life. She pointed out that the IL-1b in serum has a half-life clearance of 19 minutes, while subcutaneous administration peaks at one hour with a half-life of 1.59 minutes. Resp Ex. FFF at 4; Resp. Ex. HHH.[81] This means that any unused serum IL-1b would be inactivate for only 19 minutes after release. Resp Ex. FFF at 3. Thus, based on the data, any peripherally released IL-1b that may be elevated following vaccination has no afebrile epilepsy-causing potential. *Id.*

Dr. McCusker responded to Dr. Levin's criticisms of the literature she referenced, pointing out that Dr. Levin provided no evidence to support his opinion that brain cell cytokine levels are significantly elevated after vaccination. Resp. Ex. FFF at 3-4; Resp. Ex. GG;[82] Resp. Ex. HH.[83] She noted that in *Dubé,* they were only able to induce afebrile seizures using high levels of IL-1b injected directly into the animals' brains. *Id.* at 4; Pet. Ex. 38.[84] This does not equate to cytokines

[78] Eckerle et al., *supra* note 49.
[79] Ichiyama et al., *supra* note 15.
[80] Diane E. Griffin, *The Immune Response in Measles: Virus Control, Clearance and Protective Immunity*, 8 VIRUSES 282 (2016), filed as "Resp. Ex. GGG."
[81] Shoji Kudo et al., *Clearance and Tissue Distribution of Recombinant Human Interleukin Iß in Rats*, 50 CANCER RESEARCH 5751 (1990), filed as "Resp. Ex. HHH."
[82] Kashiwagi et al., *supra* note 53.
[83] Lin et al., *supra* note 70.
[84] Dubé et al., *supra* note 42.

generated in response to a peripheral vaccination. Resp. Ex. FFF at 4. Additionally, and contrary to Dr. Levin's opinion, *Li* showed that the cytokines released in the brain were in response to a seizure, not the cause of the seizure. Resp. Ex. FFF at 4; Resp. Ex. RR.[85]

Dr. McCusker concluded that A.L.M. suffered many infections prior to the subject vaccination that raised her proinflammatory cytokine levels as evidenced by her fevers; however, she did not develop febrile seizures or epilepsy at those times. Resp. Ex. FFF at 3. In Dr. McCusker's opinion, A.L.M. developed a seizure disorder which manifested around the age of 13 months. *Id.* at 4. There is no evidence that the vaccines A.L.M. received on October 25, 2012 contributed to the development of her seizure disorder. *Id.*

ii. The Testimony of the Experts

a. Dr. Kinsbourne

At hearing, Dr. Kinsbourne explained that his two-hit theory included genetic susceptibility as the first hit and the MMR vaccine on October 25, 2012 as the second hit triggering A.L.M.'s seizure disorder and epilepsy. Tr. 52, 67-70, 77-78. He added that both the MMR and Varicella vaccines being live attenuated vaccines fit the expected time frame of 5 to 15 days for the onset of seizures and that administering the two vaccines at the same time doubles the risk of febrile seizures. "In my mind, it says that the ability of MMR to cause seizures during the risk period, is greater if there is varicella as well." Tr. 52, 92-93. Dr. Kinsbourne stated that seizures can be triggered by a lot of different stressors or traumas in the system, including vaccination—though it is a "less prominent" cause. Tr. 79. He submitted that A.L.M.'s family history made seizures more likely. Tr. 69-70. She had susceptibility and the vaccine triggered A.L.M.'s seizures; if not for the vaccine, she may have never developed seizures. Tr. 82.

In Dr. Kinsbourne's proposed theory, the first hit was structural or genetic abnormality that existed at the location where the seizures generated from, which lowered the seizure threshold. Tr. 67-70. "Clearly, you have a lower seizure threshold if you're actually having seizure activity." Tr. 68. He described A.L.M.'s seizures as "central temporal seizures" emanating from the left hemisphere at the back of the frontal lobe or the area referred to as the central fissure, which is a cut between the frontal lobe and the other lobes. Tr. 52-53. This area is part of the motor strip involved with movements of the face and head. Tr. 53. Thus, the seizure activity arose from the face, eyes, mouth, and maybe swallowing. Tr. 53.

At hearing and for the first time, Dr. Kinsbourne suggested that A.L.M. may have been having subclinical micro seizures before her vaccinations, which lowered her seizure threshold so that the vaccines when received set off the full seizures. Tr. 69. He reasoned that in her first year of life, A.L.M. had more than the normal amount of excitatory activity – "you can think of subclinical seizures going on in that area." However, it was not until the vaccination that the area organized and caused actual seizure activity. Tr. 61. The brain is always in flux and those with a lowered seizure threshold do not immediately express seizures; it could be days, weeks, months, or never. Tr. 61-63. A.L.M. just happened to receive the October 25, 2012 vaccinations when she was most vulnerable. Tr. 63.

[85] Li et al., *supra* note 57.

Acknowledging that A.L.M.'s seizures were afebrile, Dr. Kinsbourne stated that febrile and afebrile seizures are different only as a matter of degree and can be difficult to differentiate. Tr. 65, 80. He referenced *Scheffer*[86] to illustrate that fever is not the mechanism responsible for triggering seizures where a lower seizure threshold exists. Tr. 59-60, Pet. Ex. 58.[87] *Scheffer* provided that "[v]accination triggers the onset of seizures in one-third of patients with Dravet Syndrome, some patients do not have a fever…" Tr. 59-60; Pet. Ex. 58.[88] Dravet Syndrome is a very serious seizure disorder caused by a mutation of SCN1A. Dr. Kinsbourne agreed that A.L.M. does not have Dravet Syndrome. Tr. 60. However, he claimed that *Scheffer* shows that there is a lower seizure threshold where excitation exceeds inhibition, so it takes less to provoke a seizure. Tr. 60-61; Pet. Ex. 58.[89]

Dr. Kinsbourne further stated that A.L.M.'s seizure threshold could have been so low that her seizures began before a fever had time to elevate, relying on *Scheffer* and *Berg*. Tr. 90; Pet. Ex. 58;[90] Pet. Ex. 61.[91] He submitted that A.L.M.'s seizure threshold was very low at the time of vaccination but increased at some point in time acknowledging that her seizures have ceased. Tr. 92. He stated, "central temporal epilepsies don't go on into adulthood." Tr. 92.

For the second hit, Dr. Kinsbourne opined that the MMR vaccine caused an increase in cytokines, specifically IL-1b, that triggered A.L.M.'s epilepsy. Tr. at 75. He explained that when confronted with an infection or vaccination, the innate immune system responds by sending out proinflammatory cytokines, IL-1b being the most important one. Tr. 56. The hypothalamus in the brain generates fever or inflammation in response to the cytokines, and one of the potential consequences is a seizure. Tr. 56; Pet. Ex. 37.[92] Dr. Kinsbourne conceded that fever and seizures usually go together in young children but stated there can be seizures with no fever or only a minimal rise in fever because fevers and seizures have separate pathways. Tr. 56-57. Afebrile or low-grade febrile seizures following cytokines are particularly likely if the seizure threshold is already low. Tr. 57. Fever usually has nothing to do with seizure activity. Tr. 57.

Dr. Kinsbourne stated that the literature supports afebrile seizures following vaccination.

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[86] Dravet syndrome is a rare type of epilepsy, usually starting in the first year of life. The first manifestation is often a seizure triggered by a high fever and lasting more than five minutes. Children with Dravet syndrome have other symptoms, including developmental setbacks, speech and language problems, and balance and walking issues. Cleveland Clinic, *Dravet Syndrome*, https://my.clevelandclinic.org/health/diseases/22517-dravet-syndrome.

[87] Counsel referenced Pet. Ex. 60, which is Fernando Cendes & Raman Sankar, *Vaccinations and Febrile Seizures*, 52 EPILEPSIA 23 (2011), filed as "Pet. Ex. 60" [hereinafter "Cendes & Sankar, *Vaccinations and Febrile Seizures*"]. However, Dr. Kinsbourne discussed Ingrid E. Scheffer, *Vaccination Triggers, Rather Than Causes, Seizures*, 15 EPILEPSY CURRENTS 335 (2015), filed as "Pet. Ex. 58" [hereinafter "Scheffer, *Vaccination Triggers, Rather Than Causes, Seizures*"].

[88] Scheffer, *Vaccination Triggers, Rather Than Causes, Seizures*, *supra* note 87.

[89] *Id.*

[90] *Id.*

[91] Anne T. Berg, PhD et al., *Predictors of Recurrent Febrile Seizures: A Prospective Cohort Study*, 151 ARCHIVES OF PEDIATRICS & ADOLESCENT MED. 371 (1997), filed as "Pet. Ex. 61."

[92] Vezzani et al., *supra* note 43 at 5.

Tr. 55; Pet. Ex. 33;[93] Pet. Ex. 37.[94] *Vezzani*[95] shows the release of IL-1b following a precipitating event and supports his theory. Tr. 75-76. MMR vaccine generates proinflammatory cytokines that activate the microglial in the brain, which then generated more IL-1b. Tr. 76. This process does not depend on the source of the IL-1b, but rather explains how the IL-1b causes seizure and fever independently. Tr. 76.

Dr. Kinsbourne further stated that *Dubé* illustrates how IL-1b can generate seizures and fever separately. Tr. 79. In *Dubé*, high levels of IL-1b were injected into the brains of mice to create a predisposition, mimicking genetic susceptibility. Tr. 80. However, Dr. Kinsbourne conceded that the levels of IL-1b injected into the mice's brains would not be what one would expect to see naturally occurring. Tr. 80.

Dr. Kinsbourne agreed that *Le Saux* and *von Spiczek* did not establish a causal relationship between seizures and vaccines, stating he only referenced the studies as circumstantial evidence that afebrile seizures are associated with vaccines. Tr. 82-83; Pet. Ex. 31;[96] Pet. Ex. 33.[97] He agreed the authors in *von Spiczek* looked at passive surveillance in Germany but was unsure if that surveillance process was similar to VAERS reporting in the United States. Tr. 83; Pet. Ex. 33.[98] Additionally, *von Spiczek* studied DTP vaccine and seizures. Tr. 84; Pet. Ex. 33.[99] Further, he was unsure whether the cases of afebrile seizures included all vaccines or just MMR. Tr. 84; Pet. Ex. 33.[100] His reference to *Weibel*, which studied encephalopathies, seizures, and other events following the MMR vaccine, was to show that pro-inflammatory cytokines trigger a weak point in a person. Tr. 87; Pet. Ex. 45.[101]

Dr. Kinsbourne stated that the MMR package insert contains afebrile seizures in the warnings. Tr. 58-59. He explained that after marketing a vaccine, research continues and all the reports from people who have received the vaccine are included to warn the public of what could happen. Tr. 58-59; Pet. Ex. 43. He claimed afebrile seizures would not be listed in the warning if they did not happen. Tr. at 59.

He agreed that the medical literature does not provide epidemiology or scientific certainty to suggest that the cytokines elicited by MMR vaccine can induce afebrile seizures; but for a vaccine to work, it must produce cytokines. The immune system then decides whether to mount a febrile response or not with great individual variability in the response. Tr. 66-67. He agreed that the literature supports an increase in febrile seizures within 6-14 days of MMR vaccine but claimed that epidemiology does not show the rare or random events like afebrile seizures, which is why

[93] von Spiczak et al., *supra* note 35.
[94] Vezzani et al., *supra* note 43.
[95] *Id.*
[96] Le Saux et al., *supra* note 34.
[97] von Spiczak et al., *supra* note 35. The study states "seizures may occur in temporal relationship with vaccination and concerns of a possible connection have been raised. Carefully designed studies have failed to show an association between vaccination and adverse neurologic outcome in children."
[98] *Id.*
[99] *Id.*
[100] *Id.*
[101] Weibel et al., *supra* note 50.

the Program does not require it. Tr. 73. He stated that rarity is a matter of degree—epidemiology has documented febrile seizures but just because it did not document afebrile seizures does not mean those cases don't exist. Rather, it is likely because afebrile seizures are not routinely studied. Tr. 73-74. Dr. Kinsbourne concluded that the literature he provided was sufficient proof for the Program. Tr. 66.

Discussing onset, Dr. Kinsbourne described the MMR vaccine as an unusual vaccine because it takes a week or more for the virus to assemble sufficiently in the blood stream to trigger various manifestations. Tr. 87. He opined that A.L.M.'s first seizure occurred 2-3 days after the rash and included facial movements, based on the testimony he heard that morning. Tr. 54; 72. His opinion on causation is based on onset within 5-15 days of the MMR vaccine. Tr. 84-85. However, if it is found that onset was three weeks after the November 2 rash, as stated in the VAERS report and the medical records, then he does not believe that the vaccine was the cause. Tr. 85, 91.

Dr. Kinsbourne agreed that A.L.M.'s seizures could have been coincidental, "but statistically, experientially, to my mind anyway, if something happens during a risk period, which we know that the risk of seizures is increased, then it's reasonable to say in this case that is why the seizure was generated." Tr. 63-64. He further stated that there could have been just one seizure, but seizures beget seizures. Tr. 64. Dr. Kinsbourne conceded that the onset of A.L.M.'s seizures was not intense and violent as stated in his report, but rather mysterious. Tr. 89; Pet. Ex. 14 at 3. Once controlled with Trileptal, A.L.M. had no further seizures even though she suffered from numerous febrile illnesses thereafter. Tr. 89. A.L.M.'s improved condition was either a result of antiseizure medication or the fact that seizure threshold generally rises as children get older and was not unusual. Tr. 71.

b. Dr. Levin

At hearing Dr. Levin maintained his opinion that all the vaccines A.L.M. received on October 25, 2012 caused her seizure disorder. Tr. 97. Dr. Levin agreed with Dr. Kinsbourne's two hit theory with the first hit being genetic propensity which included her family history but added "the fact of the matter is that the child had had any number of traumas, including birth trauma, which easily could be the first hit for this particular phenomena." Tr. 105-07. Dr. Levin stated that it was common sense that everyone has birth trauma, which "would be the first hit in terms of an individual who is genetically susceptible to any type of disease." Tr. 121. He later noted that A.L.M. also had double head trauma from falling off the bed and hitting her head twice before her vaccinations. Tr. 126-27.

Dr. Levin stated the vaccines A.L.M. received were the second hit and "… a substantial contributor to her disease process." Tr. 106. Further, it would be naïve to suggest that the 21 separate antigens administered to A.L.M. did not contribute to her condition and is "illogical, unscientific, and biologically ridiculous to give children all these vaccines at the same time." Tr. 97-98. Dr. Levin claimed that adverse reactions to vaccines are "very, very common and much more common that most people would like to think," and that it is not the vaccines but the manner in which they are given that increases the possibility of adverse reactions. Tr. 106. Here, 21 antigens were given at one time, "expecting them not to have an adverse reaction, that's–that's ridiculous." Tr. at 106.

According to Dr. Levin, vaccines cause the production of cytokines and cytokines cause both fever and seizures, but the two are independent of one another. Tr.96; 98-103. Dr. Levin relied on *Dubé* stating "…injection of lypopolysaccharides causes fever and also cytokine production but that the causation is independent of one another" and "the fevers and the seizures are not related and the mechanism of action is different." Dr. Levin concluded that *Dubé* proved that high levels of lypopolysaccharides evokes cytokines which then cause seizures independent of fever. Tr. 99-100; Pet. Ex. 38.[102] He quoted *Dubé* stating, "'Interestingly, nonfebrile seizures themselves led to the expression of IL-1b in microglia, suggesting that IL-1b induced seizures may, in turn, exacerbate ongoing seizures, apparently acting in its neuronal receptor.'" Tr. 100; Pet. Ex. 38.[103] He stated:

> [It] means that the lypopolysaccharides induced IL-1b–which is normal, which everybody knows—and that the IL-1b induced both fever and seizures, but sometimes it evokes only seizures, and that—we know that because Merck, Sharp & Dohme talks about it, and they're a billion dollar company and they have certainly investigated it.

Tr. 101. The fact that the studies involved injection of "high levels" of lypopolysaccharides into the animals' brains did not alter his opinion. Tr. 99; Pet. Ex. 38.[104]

I expressed my confusion, stating that my understanding of that quote was that the seizures themselves led to the expression of IL-1b in the microglia of the brain. In other words, that the seizure itself generated IL-1b, not the other way around. Tr. 101; Pet. Ex. 38.[105] Dr. Levin agreed. Tr. 101. I then asked how IL-1b generated the seizure, to which he responded, "Look at Figure 1…Doesn't that mean that cytokines cause seizures?" Tr. 101; Pet. Ex. 38.[106] Further discussion of Figure 1 ensued, with Dr. Levin stating, "The arrow points from cytokines to fever or the arrow points from cytokines to seizures, and then—and they are related, but the fact of the matter is that this particular article says that cytokines cause seizures independent of fever." Tr. 103. Dr. Levin was redirected by petitioner's counsel, who asked if *Dubé* was "suggesting that the IL-1b induced by seizures may in turn exacerbate ongoing seizures." Tr. 104; Pet. Ex. 38.[107] While agreeing that was accurate, Dr. Levin added that cytokines could cause seizures independent of fever, based not only on *Dubé* but also on "any number of articles showing that cytokines cause seizures and the mechanism by which they do, and I believe I cited many of them in my report." Tr. 104.

Respondent's counsel asked Dr. Levin why A.L.M. did not have any seizures following her other vaccinations. He replied that "you have to be appropriately susceptible at a specific time" to have a seizure. Tr. 121. Further, "…disease is a function of the exposure to an etiologic agent and the appropriately susceptible host, and at the time that she was getting vaccinated before, she just was not appropriately susceptible." Tr. 122.

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[102] Dubé et al., *supra* note 42.
[103] *Id.*
[104] *Id.* at Figure 1.
[105] *Id.*
[106] *Id.*
[107] *Id.*

Dr. Levin discussed the medical literature he claimed supported his opinion that MMR vaccine can cause afebrile seizures. Tr. 96-97. He stated that the *Ichiyama* study showed that "cytokines lead to neuronal damage, which can lead to seizures independent of whether a patient has fever." Tr. 118, 122; Pet. Ex. 39 at 2; Pet. Ex. 42.[108] He conceded that *Ichiyama* compared febrile seizures to acute encephalitis and encephalopathy and did not address afebrile seizures. Tr. 119; Pet. Ex. 42.[109] He stated that *Eriksson* stood for the proposition that seizures are the result of a reduction of endothelial cell integrity, causing edema and lowering seizure threshold. Tr. 122; Pet. Ex. 52.[110] He conceded that the *Eriksson* article made no mention of the word "seizure" or "epilepsy" and discussed endothelial cells found in the blood vessels of mouse aorta. Tr. 122-123; Pet. Ex. 52.[111] He discussed the *Eckerle* and *Weibel* articles. Tr. 112-13; Pet. Ex. 39; Pet. Ex. 41;[112] Pet. Ex. 45.[113] He confirmed that *Eckerle* discussed one case report but stated that other patients were discussed in Table 1. Tr. 113; Pet. Ex. 41.[114] He further acknowledged that *Eckerle* cautioned that it was not possible to assess a causal relationship between nonfebrile seizures and vaccinations based on the cases reviewed but added that the study was from 2013. Tr. 114; Pet. Ex. 41.[115] He acknowledged that *Weibel* studied whether a causal relationship existed between the attenuated MMR vaccine and encephalopathy of undetermined cause with permanent brain injury or death 15 days after the first dose claiming that A.L.M. "technically" had encephalopathy and concluding that "[c]onvulsive disorder is an encephalopathy."[116] Tr. 114-15; Pet. Ex. 45.[117] He agreed that the *Weibel* study was "hampered by a lack of background encephalopathic rates in unvaccinated children" and expressed difficulty studying the relationship between MMR and encephalopathy. Tr. 115; Pet. Ex. 45.[118]

In response to questions asked of him about the *Kashiwagi*[119] and *Lin*[120] articles referenced by Dr. McCusker showing that the level of cytokines released after vaccination is very low, he retorted that the fact remains that cytokines are released, and genetic propensity makes individuals respond to cytokines adversely at different times. Tr. 104-05. Cytokines can cause seizures when people are susceptible, which is what happened to A.L.M. Tr. 105.

Dr. Levin stated that the package insert for the MMR vaccine supported his opinion that the MMR vaccine is associated with afebrile seizures, pointing out that afebrile seizures are listed under "Adverse Reactions". According to Dr. Levin, this listing is a "definite indication of

[108] Ichiyama et al., *supra* note 15.
[109] *Id.*
[110] Eriksson et al., *supra* note 67.
[111] *Id.*
[112] Eckerle et al., *supra* note 49.
[113] Weibel et al., *supra* note 50.
[114] Eckerle et al., *supra* note 49.
[115] *Id.*
[116] It is important to note that Dr. Levin is the only expert who reached this conclusion. *See* Resp. Ex. YY at 4, where Dr. Holmes stated that A.L.M. did not have encephalopathy; Tr. 81-82, where Dr. Kinsbourne agreed that A.L.M. did not have an epileptic encephalopathy.
[117] Weibel et al., *supra* note 50.
[118] *Id.*
[119] Kashiwagi et al., *supra* note 53.
[120] Lin et al., *supra* note 70.

biological plausibility . . . Merck, Sharp & Dohme would not put it in there if it were not biologically plausible." Tr. 97, 115-17; Pet. Ex. 43 at 7. He acknowledged the package insert also contained the statement that adverse reactions were listed "without regard to causality." Tr. 116. When I asked him whether the package insert listed all complaints received after marketing irrespective of causation, Tr. 116-17, he responded as an attorney and a doctor:

> I can tell you Merck, Sharp & Dohme know what they're doing and wouldn't put it in their package inserts unless it was biologically plausible. And I'm sorry, but I have been an attorney and a physician, and you've only been an attorney, so that you don't necessarily understand what's going on in medicine, and that's why we have a major problem in medicine. Tr. 117-18.

Dr. Levin stated, "in the appropriately susceptible host, any vaccine can cause seizures." Tr. 119. A.L.M. received 21 antigens—three from the MMR vaccine and 18 from the other vaccinations, all of which have been documented to trigger seizures by the same mechanism proposed in this case. Vaccines cause the release of cytokines and cytokines cause afebrile seizures. Tr. 119-21. Though he did not submit any literature discussing the 18 other antigens, he stated "most of [the package inserts] talk about seizures."[121] Tr. 120. He further stated, "In medicine, the human animal responds in a uniform way to any number of different etiologic agents…the basic biology of the disease process is the same." Tr. 120.

Based on that morning's testimony, Dr. Levin stated that the temporal relationship between A.L.M.'s vaccines and the afebrile seizures 10-14 days later[122] was medically reasonable and "biologically plausible" with "no other confounding factors making it more probable than not that that vaccine caused the disease process", and but for the vaccines, A.L. M would not have had a seizure disorder. Tr. 107-08. He seemed to suggest his opinion might be different "if she had a head trauma." Tr. 108; *but see* Tr. 126. He was "aware that [A.L.M.] fell off a bed twice, that her mother brought her in to the doctor's office because she had fallen off a bed and hit her head twice." Nonetheless, based on the medical literature, medical records, testimony of the petitioner, biological plausibility, and the absence of confounding factors, Dr. Levin opined that the vaccines A.L.M. received caused or were the substantial contributing factor of her CNS abnormalities. Tr. 96.

c. Dr. Holmes

In Dr. Holmes' opinion, A.L.M. followed a typical course for epilepsy. Tr. 141. Distinguishing seizures from epilepsy, Dr. Holmes defined an epileptic seizure as a disorder of the brain that results in behavioral changes due to excessive or synchronous neuronal activity. Tr. 129. With epilepsy, there is an enduring propensity to have epileptic seizures which often includes neurobiological, cognitive, and behavioral problems, thus making it a condition much more than just seizures. Tr. 129-30. The current definition of epilepsy has changed from two or more unprovoked seizures to one unprovoked seizure and the propensity for recurrent seizures. Tr. 130.

[121] Dr. Levin did not specify whether the package inserts mention afebrile seizures.

[122] This statement conflicts with Dr. Levin's earlier statement in his expert report, which stated that seizure onset was noted to be approximately one month following A.L.M.'s vaccination. *See* Pet. Ex. 39 at 2.

Dr. Holmes described a provoked seizure as one caused by some sort of environmental stress like low blood sugar, a hit to the head, a drop in blood sodium, being over hydrated, and most commonly, fever. Tr. 141. Provoked seizures are not the same as epilepsy because in a provoked seizure, the seizures stop once the stressor is removed. Tr. 141.

Dr. Holmes explained that a seizure can be triggered in a patient with epilepsy. The literature shows that while the word "trigger" can have many meanings, it often refers to someone who already has epilepsy and something triggers a seizure. Tr. 141-42. In this way, it acts like a provoked seizure. Tr. 142. Triggers can include missed medication, fever, sleep deprivation, stress, and alcohol. Tr. 141-43. Triggers cannot cause epilepsy or damage. Triggers merely bring out the seizure in someone already predisposed to seizures, who has a lowered seizure threshold, or already diagnosed epilepsy. Tr. 144, 167. The majority of genetic epilepsies and seizures occur spontaneously with no trigger. Tr. 138, 144, 167.

Dr. Holmes stated that epilepsy can occur at any age, although it is much more common in children, and seizures come and go at certain ages based on the developmental stage of the brain. Tr. 131. Epilepsy is "time-based" and "age-based" on clinical and EEG manifestations. Tr. 131. Risk factors for epilepsy include a hypoxic-ischemic encephalopathy at birth, stroke, a history of encephalitis, meningitis, trauma, congenital brain abnormalities, and genetic or neurometabolic disorders. Tr. 132. Immunizations are not a known risk factor or cause of epilepsy. Tr. 132. Where no cause is found, the epilepsy is referred to as idiopathic, which normally refers to a genetic abnormality even if no specific gene is found. Tr. 134. This is particularly true when there is a family history of seizures. Tr. 134. About 50% of epilepsy has no definitive etiology, though the number is going down, with better MRIs capable of finding structural abnormalities and advances in gene sequencing. Tr. 135-36. Most children outgrow their epilepsy and are considered in remission, like A.L.M. who had no further seizures after weaning from medication. Tr. 133.

Dr. Holmes described febrile and afebrile seizures, explaining that febrile seizures are common and occur in about 1.5 percent of children under age 6. Tr. 170. The brain is always changing and is more excitable in children. Tr. 138-39. Febrile seizures vary in severity based on age. Tr. 139. A fever that causes a seizure in a young child will often not do the same in a 15-year-old. Tr. 139. Epilepsy, on the other hand, occurs in 0.5-1 percent of patients over the course of a lifetime. Tr. 170. Thus, when comparing the number of people with febrile seizures to the number of people with afebrile seizures or epilepsy, there will be "more people with afebrile seizures or epilepsy" because it is seen throughout patients' lives. Tr. 170.

Dr. Holmes stated febrile seizures and epilepsy are related "in some conditions." Tr. 151. He agreed with Dr. Kinsbourne's definition of febrile status epilepticus, which involves continuous seizure activity in excess of 30 minutes with high fever causing cerebral edema in the temporal lobe. Tr. 151-52. When the edema subsides, these children develop mesial temporal sclerosis and can develop a chronic epileptic condition. Tr. 152. Febrile status epilepticus is deemed acquired epilepsy due to the injury to the brain caused by the high fever and the constant seizure activity. Tr. 152. This is a very different from a simple febrile seizure. Tr. 151-52.

Dr. Holmes agreed that A.L.M. has epilepsy and disagreed that any of her vaccinations on October 25, 2012 caused or contributed to her epilepsy. Tr. 129. Dr. Holmes stated that he and his

colleagues studied the "double hit theory," or "two-hit theory" referred to by Drs. Kinsbourne and Levin. Tr. 153. In Dr. Holmes's study, a toxin was administered to animals to induce very long status epilepticus seizures, which led to intense seizures and cell injury to the brain. Tr. 153. Several weeks later, different types of seizures were induced, causing cognitive difficulties and a lower seizure threshold than if there had only been one insult. Tr. 153. The purpose of the study was to see if a child with a serious brain injury would benefit from intervention before there was a second hit, but the hypothesis did not "pan out in clinical practice." Tr. 154. He stated that the brain injury targeted in the study had to include destructive lesions that lead to the child's development of epilepsy. Tr. 154. This double hit theory does not apply to A.L.M., who did not have a destructive brain injury. Tr. 154.

Dr. Holmes agreed that A.L.M. had abnormal neuronal tissue at the location of the brain where the seizures emanated from and that she had a genetic predisposition to seizures based on family history, which could have lowered her seizure threshold. Tr. 155; 171. But a genetic propensity is not an injury per se. Rather, it means that there is a lower seizure threshold, making a person more likely than someone else to have a seizure. Tr. 142, 156. He agreed that a lower seizure threshold and seizures with a mild fever are more likely when there is a family history of febrile seizures. Tr. 142-43. But "no one's ever talked about genetic susceptibility being" the first hit, other than Dr. Kinsbourne. Tr. 154, 171. Further, Dr. Holmes disagreed that birth is a first hit, stating "that just makes no sense whatsoever." Tr. 157.

Dr. Holmes agreed if he was to assume those elements constitute "first hit," then an infection or vaccination which causes a fever could be the trigger—or second hit—that causes a seizure. Tr. 171, 176-77. However, he stated that the MMR vaccine could not cause afebrile seizures, so under the circumstances the MMR vaccine is not the second hit. Tr. 156, 173. Dr. Holmes agreed that the MMR vaccine causes an increase in cytokines, but that does not lead to an increase of cytokines in the brain, which is his problem with petitioner's theory in this case. Tr. 166. MMR vaccine can cause febrile—not afebrile—seizures in a person who has a lower seizure threshold. Tr. 166.

Dr. Holmes stated that vaccines can cause fever and the fever can provoke a seizure. Tr. 151, 168. Further, the MMR vaccine can cause febrile seizures within 14 days of vaccination and DTaP can cause febrile seizures within a couple of days of vaccination. Tr. 146. However, large studies with proper control groups have found no indication that either MMR or DTaP can cause recurrent afebrile seizures or epilepsy. Tr. 146. Further, the IOM conducted a rigorous review and did not find strong evidence for afebrile seizures following vaccination. Tr. 146. Still further, there is no support that any vaccines cause epilepsy. Tr. 146, 152. In Dr. Holmes's opinion ,A.L.M. would have gone on to have the identical course she experienced with or without the vaccine. Tr. 155-56.

Dr. Holmes further explained that fever can provoke a seizure, but the seizure is not necessarily related to the etiology of the fever. The outcome of a seizure provoked by fever is the same with and without a vaccine. Tr. 151. Dr. Holmes expressed confusion regarding Drs. Kinsbourne and Levin's opinion that seizures and fevers have two different pathways; vaccines can cause fever and fever can cause seizures; vaccines do not and cannot cause seizures without fever. Tr. 177-178. With the MMR vaccine, "…the reason you have seizures – you only have

febrile seizures with MMR because you have a fever caused by the MMR vaccine 10 to 14 days after the MMR, and that leads to the seizure." Tr. 181.

He conceded there exists one exception where vaccination may cause an afebrile seizure and that is in children with Dravet Syndrome and the seizure occurs immediately with the event, not 15 days later. Tr. 144-45, 167-68, 181-82. In these children, the afebrile seizure that occurs is considered a stress reaction and does not alter the syndrome. Tr. 145, 181-82. These same children often do not have a seizure with a subsequent vaccine. Tr. 145.

Dr. Holmes disagreed that giving several vaccines at the same time makes any difference as no vaccine has been shown to cause epilepsy. Tr. 160.

Dr. Holmes placed little importance on the rash A.L.M. reportedly developed 5-7 days after the MMR vaccine because rashes are common in young children and the rash disappeared quickly. Tr. 158-59. Dr. Holmes agreed with A.L.M.'s pediatrician that a rash was a normal reaction to vaccination. Tr. 173.

Dr. Holmes also noted that besides the transient rash A.L.M., had no sick behaviors, fever or signs of an inflammatory reaction that could cause brain damage and seizures. Tr. 159, 172-73. Further, if A.L.M. had inflammation of the brain which would involve a breakdown of the blood brain barrier, the MRIs, even those performed in 2012-2013, would have shown it. Tr. 164. However, A.L.M.'s MRIs were normal. Tr. 164-65. If there was something on her brain that was not initially picked up, it would have still been present on the subsequent MRI performed in 2015, but that MRI was normal as well. Tr. 164-65. Medication does not improve MRI results, although it may improve EEG findings. Tr. 165.

Dr. Holmes explained that EEG testing is the best at determining seizure activity. In a child, seizure severity may change due to evolving brain physiology as they get older. Tr. 140. An EEG will display spikes and sharp waves that indicate that a group of neurons is hyperexcitable, which in turn indicates that the child has not yet gone into remission. Tr. 140. If a child is on medication, an EEG is done to see if the medication can be stopped. Tr. 140. Most of the time the child is fine, but there are rare occasions where the medication is suppressing the seizures, so seizures return when the child is weaned off the medication. Tr. 140-41. Thus, it is not unusual that A.L.M.'s epilepsy went into remission as she got older, as evidenced by her normal EEG. Tr. 138-141.

To further support his opinion that the onset of A.L.M.'s epilepsy was related to the individual genetic propensity and timing, not the vaccines, Dr. Holmes pointed out that A.L.M. had many febrile illnesses before her vaccines and many illnesses in the months after her vaccines with high fevers but no seizures. Tr. 161. "I would argue that the vaccines had nothing to do with when her epilepsy emerged. I would argue that it was due to that stage of brain development, that it had nothing to do with any of the vaccines she had before." Tr. 161.

Dr. Holmes expressed his respect for Dr. Kinsbourne but disagreed that the studies Dr. Kinsbourne relied on provided any support for a vaccine causing an afebrile seizure. Tr. 168-69. Dr. Holmes again noted the exception for children with Dravet Syndrome having afebrile seizures in DTaP studies and as discussed in the studies submitted by Dr. Kinsbourne. Tr. 169, 175-76.

Cendes addressed Dravet Syndrome and the development of seizures within 2 days of DTaP vaccination. Tr. 147-48; Pet. Ex. 60.[123] The authors found that children with and without Dravet Syndrome developed seizures at the same rate and only 30-40% had seizures accompanied by fever. Tr. 148; Pet. Ex. 60.[124] These findings are evidence that the seizures were a stress response, rather than an immune response. Tr. 148, 178-79. Further, the seizures following DTaP occurred within 24 hours of vaccination not 10-14 days later, whether febrile or afebrile. Tr. 148; Pet. Ex. 60.[125] When MMR was studied, children with Dravet Syndrome had the same risk of seizures as the general population within 10-14 days following vaccination. Tr. 149. Fever was not discussed in the article. Tr. 149; Pet. Ex. 60.[126] Dr. Holmes added that the Dravet Syndrome studies also showed that the DTaP vaccine does not cause epilepsy; rather, the vaccine brought on the seizures earlier due to the underlying seizure disorder. Tr. 178. Other than this sole exception, a fever is required for a vaccine to cause a seizure, according to Dr. Holmes.[127] Tr. 178-79.

Dr. Holmes agreed that the *Le Saux* and *von Spiczak* studies involved afebrile seizures but were of limited value because they had no control group, and it was unclear how the data was entered. Tr. 149-150, Pet. Ex. 31; [128] Pet. Ex. 33.[129] Dr. Holmes disagreed that the *Scheffer* article supported the notion that afebrile seizures are caused by the MMR vaccine. Tr. 150; Pet. Ex. 58.[130] *Scheffer* was a review of the *Verbeek* study on the etiology of seizures around the time of vaccination which did not conclude that the MMR vaccine led to afebrile seizures. Tr. 15; Pet. Ex. 58.[131]

Dr. Holmes offered to go through each study relied on by Dr. Kinsbourne, but petitioner's counsel did not accept. Tr. 169-70. Dr. Holmes added, in addition to the IOM study, many review studies including a review by *Cochrane* showed no relationship between vaccines and afebrile seizures. Tr. 169-170; Resp. Ex. O.[132] Dr. Holmes added that the studies he relied on used a control group, "rigorously follow[ed] the patients for adverse events," and found no evidence that the MMR vaccine caused afebrile seizures. Tr. 176. Dr. Holmes maintained that if a seizure were to follow a vaccine, it would be because the vaccine "causes a fever, and the fever would cause the seizure. It's not anything beyond that." Tr. 176-77.

Dr. Holmes discussed the MMR vaccine package insert, noting his involvement with drug studies and explaining that package inserts contain anything that is reported following the marketing of a drug. Tr. 157-58; Pet. Ex. 43. Dr. Holmes does not dispute that the MMR vaccine can cause febrile seizures; but the fact that afebrile seizures is contained in the package insert list of adverse reactions is not an indication that the MMR vaccine can cause afebrile seizures. Tr. 158.

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[123] Cendes & Sankar, *Vaccinations and Febrile Seizures*, *supra* note 87.
[124] *Id.*
[125] *Id.*
[126] *Id.*
[127] Dr. Holmes pointed out a potential caveat to this statement: the old whole cell pertussis vaccine, which A.L.M. did not receive. Tr. 179.
[128] Le Saux et al., *supra* note 34.
[129] von Spiczak et al., *supra* note 35.
[130] Scheffer, *supra* note 87.
[131] *Id.*
[132] Demicheli et al., *supra* note 30. This is the article that Dr. Holmes referred to as the "Cochrane Review."

Dr. Holmes stated, "[T]here's a lot of things that were reported on that sheet there that I [sic] have not been subsequently shown to be associated with MMR. It's probably the worst thing you can use to try to come up with a scientific or medical decision." Tr. 158. He does not read package inserts to make any medical decisions because what is contained therein is only what someone reported—not evidence of causation stating that ". . . of our levels of evidence, I would put [package inserts] below the lowest level you could possibly have. Having it on the package insert means nothing except that someone reported it." Tr. 172.

Dr. Holmes could not put a timeframe on the onset of afebrile seizures following MMR vaccine because there is no data supporting the notion that the MMR vaccine can cause afebrile seizures. Tr. 156. He assumes the timeframe for an afebrile seizure would be consistent with what is expected for febrile seizures—within 10-14 days—though it is difficult to extrapolate due to the lack of data. Tr. 156-57. He also assumed that any time past 14 days would be too far removed to consider the afebrile seizure to be related to vaccination. Tr. 157. Dr. Holmes stated after hearing the testimony of petitioner and her sister A.L.M.'s seizure onset was roughly 10 days after the MMR vaccination, which is within the accepted range for MMR to cause febrile seizures but not afebrile seizures. Tr. 174.

In summary, Dr. Holmes stated that A.L.M.'s seizures occurred simply because she has epilepsy. Tr. 162. Genetic epilepsies start at different times because they begin spontaneously and unrelated to vaccination; otherwise, all genetic epilepsies would begin in the first few years of life. Tr. 161. Further, genetic epilepsy is not related to fever. Tr. 162. According to Dr. Holmes,

> [n]ot all epilepsy is initiated with a provoked—I can't emphasize that enough. I mean, 99 percent –98 percent of our patients that have epilepsy, it's not provoked by fever, immunizations, anything. It just occurs. They have a neurological condition called epilepsy, and it's a fundamental problem with the brain, and the immunization has nothing to do with it . . . I can't stress that enough . . . not all epilepsy begins with febrile seizures or immunization. Ninety-nine percent of it does not. There's no relationship.

Tr. 161-62.

Dr. Holmes stated that given A.L.M.'s history of high fevers and illnesses before and after her vaccinations that were not followed by seizures, the vaccines given on October 25, 2012 were merely coincident with the onset of seizures. Tr. 163. Children can have seizures or develop epilepsy at any time, and the MMR vaccine is not a trigger for afebrile seizures. Tr. 173. "…I certainly don't believe that if she had an afebrile seizure, that caused her to have epilepsy…that she would not have had epilepsy if it wasn't for that afebrile seizure. So, no, I don't buy that at all." Tr. 173.

As to alternative cause, Dr. Holmes agreed with A.L.M.'s treating physicians that her seizures were idiopathic and that she had genetic epilepsy based on her family history and her clinical course. Tr. 174-75. Succinctly stated, "A.L.M. had a genetic epilepsy that was treated effectively and went into remission and is now doing well. There is no reason whatsoever to implicate any vaccine to her clinical course." Tr. 159-160.

d. Dr. McCusker

Dr. McCusker explained that, at baseline, the immune system is always releasing low levels of cytokines into peripheral circulation. Tr. 187. Cytokines are small molecules of protein released by one cell to another with a receptor telling it what to do. Tr. 186-87. There is a difference between cytokines in peripheral circulation and cytokines in the brain. Tr. 188. Cytokine response in the peripheral immune system is tightly regulated with inflammation and counter-inflammation cytokines that turn down the immune response. Tr. 189-190. IL-1b is a preformed pro-inflammatory cytokine waiting to be activated and released when there is a threat. Tr. 190. Its role is to bring immune system cells to the area of inflammation to deal with the threat. Tr. 190. Immediately upon activation and release of IL-1b, a decoy receptor (IL-1r) is synthesized and released to shut down the threat. Tr. 190. Studies post-vaccination show low levels of IL-1b because "it is not a cytokine that circulates at any great levels in general, even in significant infections, even in patients who have very high fever." Tr. 190-91.

Dr. McCusker explained that in a steady state, brain tissue cells (glial cells and microglia) synthesize and release cytokines in the brain, which are used as neurotransmitters in the central nervous system ("CNS") to communicate pieces of information from one neuronal cell to another. Tr. 188-89. Cytokines in the CNS are released in response to trauma, like brain injury, stroke, CNS infection, or seizures. Tr. 192. IL-1b in the CNS has been shown to regulate sleep and IL-6 has been shown to play a part in short- and long-term memory. Tr. 189. Both IL-1b and IL-6 are involved in brain recovery from trauma and in pruning the neurons for learning and cognition. Tr. 189. Cytokines in the brain have specific tasks and roles in the CNS, depending on how they are released. Tr. 189.

Dr. McCusker noted although the CNS and the peripheral immune system connect, the connection is tightly regulated, and the process is different for each. Tr. 192, 207. A danger signal to the cytokines in the periphery creates inflammation, a danger signal to the cytokines in the CNS causes them to set up pathways and make responses. Tr. 207-08. Though the blood brain barrier is not complete, meaning cytokines can pass and bind to receptors in the CNS as an alert that something is going on, the cytokine stops there and cannot flood the CNS. Tr. 206. In other words, low level circulating peripheral cytokines do not have unfettered access to the CNS but can influence cytokine expression in the brain as communication molecules by stimulating the vagus nerve up to the hypothalamus to produce fever to fight infection. Tr. 192, 205-06. Fever occurs when a combination of IL-1b and/or IL-6 and/or TNFα is released at the site of an immune response. Tr. 192. For example, when a vaccine is administered in the arm or leg, IL-1b is released to the draining lymph nodes triggering nerve endings that signal up to the hypothalamus through the vagus nerve to increase body temperature. Tr. 193. Fever is one of the protective mechanisms against certain microbes that do not like to replicate at high temperatures. Tr. 193. The increased body temperature slows down the replication of the microbe and gives the immune system an opportunity to get ahead of the microbial assault. Tr. 193. The IL-1b from the periphery that triggered the "fever event" is not found in the brain, it is found in the lymph node and triggers a nerve signal up to the hypothalamus to increase body temperature to meet the threat. Tr. 193-94. The trigger is specific to the area involved in temperature regulation—the hypothalamus—not the entire brain. Tr. 193.

Dr. McCusker referenced *Kashiwagi* to show that the presence of IL-1b in the brain does not cause fever. Tr. 194-95; Resp. Ex. GG.[133] Rather,

> …you get that immune response going on in the lymph node, and that sends a signal up to the brain. Now, the degree of fever, how high the fever goes, how fast it goes up…are factors that lead to febrile seizures…it's the fever that is inducing those seizures. It's not that IL-1b, in the brain, is inducing those seizures, and that's really a key element here, because we know from the febrile seizure story that circulating IL-1b is actually. . . undetectable in the *Kashiwagi* articles.

Tr. 195-96. In summary, the circulating cytokines signal from the lymph node to the brain at the hypothalamus to change the body temperature and the rise in temperature leads to the seizure. Tr. 196-98; Resp. Ex. GG.[134]

Dr. McCusker discussed the literature relied on by Dr. Kinsbourne, noting that in *Dubé* large amounts of IL-1b were injected directly into the brains of the animals but hyperthermia also needed to be induced to result in seizures. Tr. 194-95, 208; Pet. Ex. 38.[135] *Dubé* also showed that IL-1b sits in the CNS all the time communicating and damage in the CNS from a CNS infection, trauma, or post-seizure event increases the cytokines in the brain cells, not in the periphery. Tr. 208, 210; Pet. Ex. 38.[136] *Li* and *Vezzani* discussed chronic epilepsy in animals and showed that cytokines released after brain trauma, damage, or inflammation act to repair damage, but if the seizures or trauma continues, it will significantly lower the seizure threshold over time. Tr. 211; Resp. Ex. RR;[137] Resp. Ex. SS.[138] Therefore, in the CNS ". . . you have your trauma, you have your seizure. The seizure causes damage, the damage releases IL-1b. The IL-1b tries to contain the damage, the damage is not contained, but now the IL-1b is still being produced…now it's acting to change the seizure threshold within the animals." Tr. 211-12, Resp. Ex. RR;[139] Resp. Ex. SS.[140] In the animal models where the IL-1b was injected systemically similar to circulating cytokines, there was an anti-convulsant effect as opposed to a pro-convulsant. Tr. 204. Thus, "if you had this increase in peripheral IL-1b, mimicking what they did in the animals, and you had a patient who had a predisposition to developing seizures," the circulating IL-1b in the periphery would actually lower the risk of seizures rather than increase it, suggesting that the release of regulatory molecules immediately after the release of cytokines causes a net decrease in functional IL-1b. Tr. 204-05. This, Dr. McCusker stated, is one of her problems with petitioner's theory. Tr. 212.

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[133] Kashiwagi et al., *supra* note 53.
[134] *Id.*
[135] Dubé et al., *supra* note 42.
[136] *Id.*
[137] Li et al., *supra* note 57.
[138] Annamaria Vezzani et al., *Powerful Anticonvulsant Action of IL-1 Receptor Antagonist on Intracerebral Injection and Astrocytic Overexpression in Mice*, 97 PROCEEDINGS OF THE NAT'L ACAD. OF SCIENCES 11,534 (2000), filed as "Resp. Ex. SS."
[139] Li et al., *supra* note 57.
[140] Vezzani et al., *supra* note 138.

Another problem with petitioner's theory is that the half-life for active peripherally circulating IL-1b has been shown in studies to be 19 minutes, after which they start to lose their activity significantly. Tr. 215; Resp. Ex. HHH.[141] There are no cytokines present two weeks or even five days after vaccination. Tr. 229. Petitioner's theory revolves around a cytokine-mediated lowering of seizure threshold, which would have occurred immediately after vaccination if it occurred at all. Tr. 229. Therefore, the vaccine cannot be responsible here because, at the earliest, the seizures occurred approximately two weeks after vaccination. Tr. 229.

Dr. McCusker discussed A.L.M.'s rash on November 2, noting the difference between live and killed vaccines and the body's reaction to both. Tr. 199-200. In killed vaccines, all cytokines, not just IL-1b, are transiently elevated to a level just high enough to kick off an inflammatory event. The inflammatory event is localized in the draining lymph nodes close to the vaccination site for the first two to three days, then the immune response circulates beyond the lymph nodes. Tr. 200. In a live attenuated vaccine, the virus needs time to replicate so the response is not strong in the first several days. Tr. 200-01. As the virus starts replicating, the immune system turns on regulatory T cells, which causes a rash if any to occur 7-10 days after the MMR vaccine. Tr. 201, 227. *Lin* studied wild type measles infection with a co-infection of HIV-1 and found increases in IL-1b in the peripheral blood at the time the rash started but maxing out at a very low level. Tr. 202-03; Resp. Ex. HH.[142] IL-1b levels would be the same or even lower with the vaccine. Tr. 203. *Griffin* showed that the rash following wild measles infection signaled the end of the immune response, indicating that the virus is under control. Tr. 201, 226-27; Resp. Ex. GGG;[143] *see also* Resp. Ex. EE.[144] Accordingly, if A.L.M.'s rash was a measles rash and the literature is correct, the rash would have signaled the completion of the inflammatory process, after which point cytokines were no longer active. Tr. 227, 229. Even if A.L.M. had a low-grade fever when she developed the rash, the cytokine level in the periphery would still be low. Tr. 214-15. For that reason, Dr. McCusker was unable to "connect the dots" for petitioner's theory in this case. Tr. 214-15.

Dr. McCusker stated that the MMR vaccine can cause fever and the fever can cause a seizure, but the degree of fever necessary to cause a seizure would also cause other symptoms. Tr. 218. Further, the mechanism for febrile and afebrile seizures is different and a predisposition, trauma, stroke, meningitis, or encephalitis is required for an afebrile seizure. Tr. 222-23. A.L.M. had afebrile seizures which then disappeared and were not exacerbated by subsequent febrile events or infections. Tr. 219. Dr. McCusker stated that if the hypothesis is that the MMR vaccine raised the IL-1b to a high enough level to lower the seizure threshold, then she would have expected that A.L.M.'s subsequent fevers and infections would lead to the same sequence of events. Tr. 219. However, that was not the case here. Tr. 219.

Dr. McCusker disagreed that A.L.M. was having mini seizures prior to her vaccinations, causing her brain to release IL-1b and lowering her seizure threshold. Tr. 213. Even assuming that she was having mini seizures, Dr. McCusker claimed that A.L.M.'s receipt of MMR and Varicella, two live attenuated vaccines, would not "throw the IL-1b over the top," adding that vaccination alone is "not sufficient to trigger a seizure [even] in a predisposed host." Tr. 223. The IL-1b levels

[141] Kudo et al., *supra* note 81.
[142] Lin et al., *supra* note 70.
[143] Griffin, *supra* note 80.
[144] Oliveira et al., *supra* note 64.

produced by vaccines are "infinitesimally lower than" what is necessary to induce seizures. Tr. 213. Perhaps this would be a persuasive theory if high enough amounts of cytokines were injected directly into A.L.M.'s lateral ventricles. Tr. 236. The data suggests that elevating IL-1b in the periphery increases seizure threshold and patients are less likely to seize in that context, so "it goes against [petitioner's] hypothesis." Tr. 236, 246-48. Further, Dr. McCusker stated that if she were to assume that A.L.M. was having micro seizures and that IL-1b was sufficient to induce seizures, then the onset of seizures would have occurred quickly after the DTaP vaccine because it would have produced a larger cytokine release, according to *Kashiwagi*. Tr. 213-14; Resp. Ex. GG.[145] Dr. McCusker detailed the sickness behaviors associated with high level of cytokines, noting that A.L.M. was asymptomatic, had afebrile seizures, and demonstrated no symptoms indicative of high levels of circulating cytokines. Tr. 214, 237-38. Finally, there is no evidence in the record that A.L.M. was having micro or mini seizures. Tr. 250.

Petitioner's counsel then suggested that perhaps A.L.M.'s innate immune system was not working correctly, as evidenced by A.L.M.'s genetic predisposition to seizures. Tr. 236-37. Dr. McCusker stated what counsel was suggesting was a disease called periodic fever syndrome in the IL-1b or TNF-alpha pathways which results in high fevers without provocation. Tr. 237. There is no evidence in the record suggesting that A.L.M. suffered from this disease or a defect in her IL-1b regulatory pathway. Tr. 237. Any fevers A.L.M. suffered prior to her vaccinations were from normal febrile illnesses and not indicative of periodic fever syndrome. Tr. 237.

Dr. McCusker was asked if the receipt of 8 vaccines would constitute sufficient stress to cause a seizure. Tr. 232. She explained that she believed the reference by Dr. Holmes to stress was an immediate stressful event such as a blood draw or needle in a child with a seizure predisposition who then had a vasovagal response or a seizure when they saw the needle, for example. Tr. 232-33. Vaccinations activate the immune system, and the activation leads to a cascade of events, but whether that cascade is sufficient to cause seizures is another issue. Tr. 233.

Dr. McCusker referenced large trials involving thousands of vaccines given to children in A.L.M.'s age group that showed a background rate of seizure disorder onset within 10, 30, or 60 days of vaccinations. Tr. 220-21; *see* Resp. Ex. M;[146] Resp. Ex. N.[147] The trials did not implicate vaccines and demonstrated that seizures would still occur in these children, even without vaccination. Tr. 220-21. The link to vaccines was only temporal. Tr. 220-221. Based in part on these results, Dr. McCusker argued that A.L.M.'s clinical course was entirely consistent with "what happens when children develop seizure disorders." Tr. 221.

Dr. McCusker discussed the package insert for the MMR vaccine, stating that the information is dictated by the FDA, not the vaccine manufacturer. Tr. 230; Pet. Ex. 43. Like Dr. Holmes, she stated that all reports during clinical trials and post-marketing are included in the insert according to the rules, but it is not an indication of causation. Tr. 230. For example, there is nothing in MMR vaccine that would cause pneumonia, but if there were reports of pneumonia during the clinical trials or post-marketing period, pneumonia would be listed in the package insert. Tr. 230-31.

[145] Kashiwagi et al., *supra* note 53.
[146] Davis & Barlow, *supra* note 28.
[147] Barlow et al., *supra* note 29.

Dr. McCusker stated that the mechanism proposed in this case makes no biological sense; it relies on IL-1b but does not link the increase of IL-1b following vaccination to the seizure disorder A.L.M. subsequently presented with. Tr. 221. Petitioner failed to explain how a normal immune response to the MMRV could generate an inflammatory event that led to a change in the predisposition of her CNS. Tr. 224. Research shows that the only way that change occurs is by injecting high levels of cytokines directly into the ventricles of animals, moments before hypothermia, a stimulus for seizures, was introduced. Tr. 224. The stimulus must be introduced immediately after injecting high levels of cytokines because, after twenty minutes, the cytokines are gone. Tr. 224. From "a mechanistic standpoint, I can't put A and B together." Tr. 224. Also, with a cytokine level high enough to cause seizures, one would not expect to see a healthy child. Tr. 225. Rather, the child would be experiencing a cytokine storm, which causes marrow and kidney failure and a decrease in white blood cells. Tr. 225. A.L.M. did not "fit the picture of child with rampant circulation of cytokines." Tr. 225.

Dr. McCusker aptly posed the question, getting at the heart of this matter, "other than timing, is there anything that says the vaccine could cause or did cause this seizure disorder in this child?" Tr. 220. Like Dr. Holmes, she opined that the seizures would have manifested in A.L.M. regardless of vaccination and the timing is a mere coincidence. Tr. 220.

VI. Applicable Law

A. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *See Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352 (Fed. Cir. 1999).[148]

To prove causation for an "off-Table" injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen*

[148] The Vaccine Act also requires petitioners to show by preponderant evidence the vaccinee suffered from the "residual effects or complications" of the alleged vaccine-related injury for more than six months, died from the alleged vaccine-related injury, or required inpatient hospitalization and surgical intervention as a result of the alleged vaccine-related injury. § 11(c)(1)(D). It is undisputed that this requirement is satisfied in this case.

requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioner to provide a sound and reliable medical theory demonstrating that the vaccines received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted); *Knudsen*, 35 F.3d at 548. This theory need only be "legally probable, not medically or scientifically certain." *Pafford*, 451 F.3d at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs.,* 569 F.3d 1367, 1380 (Fed. Cir. 2009). Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases may be enough to satisfy *Althen* prong one" (emphasis in original)). But this does not negate or reduce a petitioner's ultimate burden to establish his entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted). Nonetheless, although petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" (*Capizzano*, 440 F.3d at 1325), the special master may consider and evaluate such evidence when filed. *Andreu*, 569 F.3d at 1379 (Special masters may consider medical literature and epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury."). Further, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs*., 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs*., 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). A sound and reliable "medical or scientific explanation must support this logical sequence of cause and effect," *id.* at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination

was the reason for the injury," *Paluck v. Sec'y of Health & Human Servs*., 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375 (Fed. Cir. 2009)). Petitioner is not, however, required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs*., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of eliminating alternative independent potential causes").

To satisfy the third *Althen* prong, petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs*., 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

B. Legal Standard Regarding Fact Finding

The process for making determinations in Vaccine Program cases regarding factual issues begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are generally considered to be more trustworthy. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993); *but see Kirby v. Sec'y of Health & Human Servs.*, 993 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying that *Cucuras* does not stand for proposition that medical records are presumptively accurate and complete). While not presumed to be complete and accurate, medical records made while seeking treatment are generally afforded more weight than statements made by petitioner after-the-fact. *See Gerami v. Sec'y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013) (finding that contemporaneously documented medical evidence was more persuasive than the letter prepared for litigation purposes), *mot. for rev. denied*, 127 Fed. Cl. 299 (2014). Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948).

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining facts such as the onset of a petitioner's symptoms. *Vallenzuela v. Sec'y of Health & Human Servs.*, No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); *see also Eng v. Sec'y of Health & Human Servs.*, No. 90-175V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb 18, 1994) (explaining that § 13(b)(2) "must be construed so as to give effect to § 13(b)(1) which directs the special master or court to consider the medical record...but does not require the special master or court to be bound by them"); *see also Burns v. Sec'y of Health & Human Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993) (holding that it is within the special master's discretion to determine whether to afford greater weight to medical records or to other evidence,

such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is rational).

There are situations in which compelling oral testimony may be more persuasive than written records. *See Campbell*, 69 Fed. Cl. at 779. When witness testimony contradicts medical records, such testimony must be consistent, clear, cogent, and compelling to be persuasive. *See Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (vacated on other grounds, *Sanchez by & through Sanchez v. Sec'y of Health & Human Servs.*, No. 2019-1753, 2020 WL 1685554 (Fed. Cir. Apr. 7, 2020), *review denied, Sanchez by & through Sanchez v. Sec'y of Health & Hum. Servs*., 152 Fed. Cl. 782 (2021)) (quoting *Blutstein v. Sec'y of Health & Human Servs.*, No. 90-2808V, 1998 WL 408611, at *85 (Fed. Cl. Spec. Mstr. June 30, 1998)); *see, e.g.*, *Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). Special masters may also consider other types of evidence, such as unsworn statements, on the grounds that the Vaccine Program was designed to have "flexible and informal standards of admissibility of evidence." 42 U.S.C. § 300aa-12(d)(2)(B); *see also Munn v. Sec'y of Health & Human Servs*., 970 F.2d 863, 873 (Fed. Cir. 1992).

On the whole, a special master's fact findings are to be upheld when the special master's evaluation is evidence-based and not wholly implausible. *See Colon v. Sec'y of Health & Human Servs.*, 156 Fed. Cl. 534 (2021).

C. Evaluating Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of their claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc*., 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id.* at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the weighing of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the ipse dixit of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Because a determination regarding whether petitioner has met her burden in proving that A.L.M.'s vaccinations were the cause-in-fact of her afebrile seizures and epilepsy hinges in part on the opinions of Drs. Kinsbourne and Levin and Drs. Holmes and McCusker, it is necessary to address their qualifications and their relative expertise before weighing the value of their opinions. *See Depena v. Sec'y of Health & Hum. Servs*., No. 13-675V, 2017 WL 1075101 (Fed. Cl. Spec. Mstr. Feb. 22, 2017), *mot. for rev. denied*, 133 Fed. Cl. 535, 547-48 (2017), *aff'd without op*., 730 Fed. App'x 938 (Fed. Cir. 2018); *Copenhaver v. Sec'y of Health & Hum. Servs*., No. 13-1002V, 2016 WL 3456436 (Fed. Cl. Spec. Mstr. May 31, 2016), *mot. for rev. denied*, 129 Fed. Cl. 176 (2016).

Dr. Levin is board-certified in immunology but has not practiced clinical medicine since the 1990s. Tr. 110, 111. Rather, he primarily practices law. Tr. 109. Dr. Levin's lack of recent medical practice has contributed to special masters' criticism of his work in previous Vaccine Program cases. *See, e.g., Martin v. Sec'y of Health & Hum. Servs*., No. 15-789V, 2020 WL 4197748, at *31 (Fed. Cl. Spec. Mstr. May 8, 2020) (describing Dr. Levin as "an expert out of his depth"); *Bigbee v. Sec'y of Health & Hum. Servs*., No. 06-663V, 2012 WL 1237759, at *30, 36 (Fed. Cl. Spec. Mstr. Mar. 22, 2012) (discrediting Dr. Levin's "cytokine storm" theory and noting that Dr. Levin "ha[s] not see[n] a patient since 1993" and "has not performed an autopsy on a child since the 1980's"); *Doe/11 v. Sec'y of Health & Hum. Servs*., No. 99-212V, 2008 WL 4899356, at *8-9 (Fed. Cl. Spec. Mstr. Oct. 29, 2008) (rejecting Dr. Levin's theory that a vaccine-induced cytokine response led to brain inflammation and caused a child's death), *mot. for rev. denied*, 87 Fed. Cl. 1 (2009), *aff'd*, 601 F.3d 1349 (Fed. Cir. 2011).

In contrast, Dr. McCusker is both a clinical medical provider and associate professor, in addition to being the Division Director of Pediatric Allergy, Immunology and Dermatology at the Montreal Children's Hospital. Tr. 185. Further, she conducts research focused on the regulation of immune responses at the Meakins-Christie Labs of McGill University. Resp. Ex. AA at 20. Dr. McCusker's medical opinions have been credited in several Vaccine Program cases. *See, e.g., Martin*, 2020 WL 4197748, at *31 (stating that Dr. Levin's "credentials as an immunologist were far outweighed by Dr. McCusker's"); *Bigbee*, 2012 WL 1237759, at *35 (describing Dr. McCusker's testimony regarding the role of cytokines during vaccination as "highly persuasive").

Dr. McCusker's extensive clinical work in the field of immunology vastly outweighs Dr. Levin's. Though Dr. Levin's certifications and focus areas of research are relevant, Dr. McCusker's immense clinical experience and specialty in pediatric immunology make her particularly qualified to opine on this case. This disparity in qualifications contributes to the evaluation of the evidence under the three *Althen* prongs.

Drs. Kinsbourne and Holmes are both well respected pediatric neurologists. However, Dr. Kinsbourne has not been in clinical practice since the 1990s. Tr. 72-73. Dr. Holmes, on the other hand, routinely cares for children with epilepsy in his clinical practice. Further, Dr. Kinsbourne has previously been unsuccessful in opining that a vaccine can cause afebrile seizures. *See, e.g., Dodd v. Sec'y of Health & Human Servs*., No. 09–0585V, 2013 WL 3233210, at *2, 4, 7-8 (Fed. Cl. Spec. Mstr. June 5, 2013) (ruling against entitlement where Dr. Kinsbourne opined that the MMR vaccine caused an afebrile seizure and seizure disorder). Though he has added literature in

support of his theory, none of the additional literature lends any support to the theory that the MMR vaccine—or any vaccine—can cause afebrile seizures leading to epilepsy.[149]

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs*., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs*., 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VII. *Althen* Analysis

Because petitioner does not allege an injury listed on the Vaccine Injury Table, her claim is classified as "off-Table." As noted above, for petitioner to prevail on an "off-Table" claim, she must submit a sound and reliable theory that A.L.M.'s afebrile seizures and epilepsy were caused by the MMR and/or Varicella vaccines received on October 25, 2012. *Capizzano*, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that the injury was caused by factors unrelated to the vaccinations. *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs*., 717 F.3d 1363, 1367 (Fed. Cir. 2013).

A. *Althen* Prong One: Petitioner has not Proffered a Sound and Reliable Medical Theory

Prong I analyzes whether MMR vaccine can cause afebrile seizures and/or epilepsy.

Drs. Kinsbourne and Levin opine, with some variation, that the MMR or all the vaccines administered on October 25, 2012, can cause afebrile seizures and/or epilepsy. Both propose a two-hit theory. The first hit is the existence of a latent brain abnormality causing an hyperexcitable neural network which lowers the seizure threshold. Pet. Ex. 14 at 4-7; Pet. Ex. 39 at 2. The second hit is the MMR vaccine or all the vaccines administered on October 25, 2012. Pet. Ex. 21 at 4, 5; Pet. Ex. 39 at 1. Drs. Kinsbourne and Levin submit that the IL-1b that is released following receipt of vaccines has the propensity to cause both febrile and afebrile seizures, as well as epilepsy. Tr. 64; Pet. Ex. 14 at 6-7; Pet. Ex. 39 at 2; Pet. Ex. 21 at 5; *see* Pet. Ex. 25;[150] Pet. Ex. 34.[151]

In Dr. Kinsbourne's opinion, IL-1b, which is generated during a normal response to vaccines, can cause both seizures and fevers, but one is not contingent on the other. Pet. Ex. 36 at 2; Pet. Ex. 38.[152] He submitted that the *Dubé* study showed that IL-1b causes fever, but the

[149] As stated elsewhere in this decision, the literature does support afebrile seizures following DTaP vaccine within 24 hours in children with Dravet's Syndrome, which is a significant brain injury and a condition that A.L.M. fortunately does not have.
[150] Iwasaki & Medzhitov, *supra* note 26.
[151] Vezzani & Baram, *supra* note 27.
[152] Dubé et al., *supra* note 42.

epileptogenic effect of IL-beta is not mediated by its propensity also to elevate body temperature. Pet Ex. 21 at 5; Pet. Ex. 38.[153] He added that *Vezzani* also showed that IL-1beta generates epileptogenesis through different pathways, neither of which includes fever. Pet. Ex. 36 at 2; Pet. Ex. 37.[154]

Dr. Kinsbourne agreed that fever is generally associated with seizures but stated "substantial literature" supports afebrile seizures occurring in the risk period after MMR. Pet. Ex. 21 at 5. He submitted *Le Saux* and *von Spiczak* as support for afebrile seizures following the MMR vaccine. *Id*; Pet. Ex. 31;[155] Pet. Ex. 33.[156] He recognized that the IOM did not credit these reports but claimed that the IOM hardly credits any causal relations between any vaccine and any adverse event. Pet. Ex. 21 at 5.

Dr. Kinsbourne concluded that a pre-existing brain abnormality, causing hyperexcitable neuronal tissue in that focal area of the brain, lowered the seizure threshold rendering it susceptible to a triggering event. Pet. Ex. 14 at 4-5; Pet. Ex. 21 at 6. The second hit or triggering event was the MMR vaccine, which released pro-inflammatory cytokines, specifically IL-1beta, causing afebrile seizures. Pet. Ex. 16 at 2; Pet. Ex. 21 at 6.

Dr. Levin proposed that the first hit was a host of traumas to the brain, including birth trauma, family history, genetic propensity, and double head trauma, which lowered the seizure threshold. Pet. Ex. 39 at 2; Tr. 106-07, 126-27. He then claimed that the 21 separate infectious antigens and adjuvants contained in all the vaccines A.L.M. received that day[157] caused neuronal damage which then caused afebrile seizures. Tr. 97, 119-20; Pet. Ex. 39 at 1-2. Dr. Levin proposed that the rash on November 2, 2012 was consistent with a cytokine-induced inflammatory cutaneous reaction. Pet. Ex. 39 at 2; Pet. Ex. 50 at 1.

Dr. Levin relied on several studies to support his opinion that vaccines can cause afebrile seizures. Pet. Ex. 39 at 2; Pet. Ex. 50 at 1-2; *see* Pet. Ex. 38;[158] Pet. Ex. 41;[159] Pet. Ex. 42;[160] Pet. Ex. 45;[161] Pet. Ex. 52;[162] Pet. Ex. 55.[163] When questioned about the literature, he conceded that *Ichiyama* compared prolonged febrile seizures to acute encephalitis and encephalopathy but did not address afebrile seizures. Tr. 118-19; Pet. Ex. 42.[164] He acknowledged that *Eckerle* was a case study and the authors concluded it was not possible to assess a causal relationship between afebrile seizures and vaccinations. Tr. 113-14; Pet. Ex. 41.[165] It was also noted that *Weibel* examined

[153] *Id.*
[154] Vezzani et al., *supra* note 43.
[155] Le Saux et al., *supra* note 34.
[156] von Spiczak et al., *supra* note 35.
[157] A.L.M. received the MMR, DTaP, Hib, Prevnar 13, and Varicella vaccinations on October 25, 2012. Pet. Ex. 1 at 1.
[158] Dubé et al., *supra* note 42.
[159] Eckerle et al., *supra* note 49.
[160] Ichiyama et al., *supra* note 15.
[161] Weibel et al., *supra* note 50.
[162] Eriksson et al., *supra* note 67.
[163] Vezzani et al., *supra* note 66.
[164] Ichiyama et al., *supra* note 15.
[165] Eckerle et al., *supra* note 49.

whether a causal relationship existed between the attenuated MMR vaccine and encephalopathy of undetermined cause with permanent brain injury or death 15 days after the first dose. It did not address afebrile seizures. Tr. 114-15; Pet. Ex. 45.[166] Dr. Levin then claimed that there was an encephalopathy in this case. Tr. 114-15. Finally, he conceded that *Eriksson* also made no mention of seizures or epilepsy. Tr. 122-23; Pet. Ex. 52.[167]

Further, Dr. Levin stated *Dubé* proved that high levels of lypopolysaccharides evoke cytokines that cause seizures independent of fever because the "mechanism of action is different." Tr. 99-103; Pet. Ex. 38.[168] He quoted *Dubé,* "'… nonfebrile seizures themselves led to the expression of IL-1b in microglia, suggesting that IL-1b induced seizures may, in turn, exacerbate ongoing seizures, apparently acting in its neuronal receptor,'" Tr. 100; Pet. Ex. 38,[169] interpreting this as:

> [It] means that the lypopolysaccharides induced IL-1b–which is normal, which everybody knows—and that the IL-1b induced both fever and seizures, but sometimes it evokes only seizures, and that—we know that because Merck, Sharp & Dohme talks about it, and they're a billion dollar company and they have certainly investigated it. Tr. 101.

I expressed my confusion with his interpretation, stating that I understood *Dubé* to mean that the seizures themselves led to the expression of IL-1b in the microglia of the brain, or in other words, that the seizure itself generated IL-1b—not the other way around. Tr. 101; Pet. Ex. 38.[170] Dr. Levin agreed, but pointed to Figure 1 stating, "The arrow points from cytokines to fever or the arrow points from cytokines to seizures, and then—and they are related, but the fact of the matter is that this particular article says that cytokines cause seizures independent of fever." Tr. 101, 103. Even after agreeing with petitioner's counsel that *Dubé* was "suggesting that the IL-1b induced by seizures may in turn exacerbate ongoing seizures," Dr. Levin added that cytokines could cause seizures independent of fever based not only on *Dubé,* but also on "any number of articles showing that cytokines cause seizures and the mechanism by which they do, and I believe I cited many of them in my report." Tr. 104; Pet. Ex. 38.[171] He agreed that *Vezzani* shows that seizures lead to the expression of IL-1beta in microglia of the brain, suggesting that IL-1beta induced by seizures may in turn exacerbate ongoing seizures. Pet. Ex. 50 at 1; Pet. Ex. 55.[172]

Dr. Levin added that the MMR package insert lists afebrile seizures on its list of Adverse Reactions as proof of causation, stating it would not be on the package insert if it were not "biologically plausible."[173] Tr. 115-18; Pet. Ex. 43 at 7.

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[166] Weibel et al., *supra* note 50.
[167] Eriksson et al., *supra* note 67.
[168] Dubé et al., *supra* note 42.
[169] *Id.*
[170] *Id.*
[171] *Id.*
[172] Vezzani et al., *supra* note 66.
[173] Special masters have not given manufacturers' package inserts much weight. In a leading case, one special master went so far as to declare that "federal regulations specifically preclude the contents of drug product labels, as reproduced in the [Physician's Desk Reference], from serving as admissions regarding

Dr. Levin opined that all the vaccines A.L.M. received on October 25, 2012 caused a release of cytokines, specifically IL-1b, which resulted in neuronal damage, and the neuronal damage then caused afebrile seizures and epilepsy. Pet. Ex. 39 at 1-2. The fact that the *Dubé* study involved injection of "high levels" of lypopolysaccharides directly into the brains of animals did not alter his opinion. Tr. 99; Pet. Ex. 38.[174] His opinion was also not swayed by the *Kashiwagi* and *Lin* articles relied on by Dr. McCusker, showing that the level of cytokines released after vaccination are very low. Tr. 104-05. Dr. Levin stated the facts remain that cytokines are released and can cause seizures in susceptible people, and genetic propensity makes individuals respond adversely at different times. Tr. 105. The "mechanism" and/or pathways for how cytokines or specifically could cause afebrile seizures was not provided.

In contrast, respondent's experts claimed that vaccines cannot cause afebrile seizures or epilepsy. Tr. 146, 169-170, 176.

Dr. Holmes opined vaccines cannot cause afebrile seizures or epilepsy. Resp. Ex. A at 7. Epilepsy is most common in children and there are multiple risk factors for epilepsy, but immunization is not one. Tr. 131-32. The majority of genetic epilepsies occur spontaneously with no trigger. Tr. 138. Roughly 50% of epilepsy has no definitive etiology. Tr. 135-36. Most children outgrow their epilepsy. Tr. 133.

Further, there is no evidence epidemiologically or mechanistically to support an MMR vaccine causing afebrile seizures. Resp. Ex. V at 2-3. Dr. Holmes agreed vaccines elicit an innate immune response, explaining that within hours of the introduction of an antigen to the body, an

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causation." *Werderitsch v. Sec'y of Health & Human Servs*., No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005). Relying upon regulations found at 21 C.F.R. § 600.80, *Werderitsch* reasoned that because the Food and Drug Administration requires manufacturers to list adverse occurrences regardless of causality, the listing of an event on a product insert does not support a finding of causation. Other cases declining to rely upon package inserts to support a finding of causation include: *Salerno v. Sec'y of Health & Human Servs*., No. 16-1280, 2020 WL 344163, at *13 (Fed. Cl. Spec. Mstr. May 29, 2020); *Bender v. Sec'y of Health & Human Servs*., No. 11-693V, 2018 WL 3679637, at *31 (Fed. Cl. Spec. Mstr. July 2, 2018) (noting that "vaccine package inserts do not constitute causation evidence meriting significant weight"), *mot. for rev. denied*, 141 Fed. Cl. 262 (2019); *Tompkins v. Sec'y of Health & Human Servs*., No. 10-261V, 2013 WL 3498652, at *14 (Fed. Cl. Spec. Mstr. June 21, 2013) (citing the testimony of petitioner's expert who acknowledged that reports in package inserts "may reflect a temporal relationship between vaccine and illness"), *mot. for rev. denied*, 117 Fed. Cl. 713 (2014); *Coppola v. Sec'y of Health & Human Servs*., No. 09-631V, 2012 WL 1118849, at *26 (Fed. Cl. Spec. Mstr. Mar. 7, 2012) (rejecting a petitioner's reliance on vaccine package insert information as indicative of alleged vaccine causation); *Doe v. Sec'y of Health & Human Servs*., No. 99-670V, 2004 WL 3321302, at *14 (Fed. Cl. Spec. Mstr. Oct. 5, 2004) (finding that petitioner failed to establish that hepatitis B vaccine can cause chronic fatigue syndrome although the package insert listed several symptoms petitioner experienced). *But see Russell v. Sec'y of Health & Human Servs*., No. 11-0282V, 2014 WL 4922194, at *7 (Fed. Cl. Spec. Mstr. Sept. 9, 2014) (giving some weight to a manufacturer's report of an adverse event "judged to be vaccine related by the study investigator" but still finding that petitioner failed to meet the burden regarding prong 1). In accord with these persuasive (though not binding) precedents, the undersigned declines to give the manufacturer's package insert more weight than the epidemiologic studies.

[174] Dubé et al., *supra* note 42 at Figure 1.

innate immune response occurs where T cells release inflammatory cytokines that amplify the immune response, ultimately leading to desired immunity. Resp. Ex. YY at 3. Dr. Holmes agreed the MMR vaccine can cause febrile seizures within 14 days of vaccination. Tr. 145-46. But, when "…we can talk about MMR, and the reason you have seizures – you only have febrile seizures with MMR because you have a fever caused by the MMR vaccine 10 to 14 days after the MMR, and that leads to the seizure." Tr. 181.

Dr. Holmes stated that large studies with proper control groups, including a review by *Cochrane*, demonstrated no relationship between vaccines and afebrile seizures. Tr. 146, 169-170, 176; *see* Resp. Ex. M;[175] Resp. Ex. N;[176] Resp. Ex. O.[177] Dr. Holmes explained that vaccines can cause fever, and fever can cause a seizure, but vaccines themselves cannot cause seizures. Tr. 151, 176-78. There is no proof that a normal immune response to vaccines can result in neurological injury as alleged by petitioner's experts. Resp. Ex. YY at 3.

Dr. Holmes addressed the "double hit theory," or "two-hit theory." He agreed that a genetic predisposition could lower seizure threshold and that the MMR vaccine causes increased cytokines, but he claimed a person with a lower seizure threshold would have a febrile not afebrile seizure following the MMR vaccine. He maintained that MMR vaccine cannot cause afebrile seizures. Tr. 156-57, 166, 171. Dr. Holmes referenced the *McIntosh* study,[178] to show the limited exception where DTaP has been associated with afebrile seizures in children with Dravet Syndrome, but it was not the vaccine but rather a stress reaction in those children that provoked afebrile seizures. Tr. 147-48, 175-76. Other than that limited exception, there must be a fever for a vaccine to cause a seizure. Tr. 179.

Dr. Holmes took issue with petitioner's experts' opinion that cytokines produced from peripheral vaccinations can cause both fever and seizures independent of one another, claiming that the articles they relied on did not reach such a conclusion and no mechanism for how this can happen was provided. Resp. Ex. V at 2-3; Resp. Ex. YY at 4. Addressing the literature relied on by petitioners, Dr. Holmes stated that *Ichiyama* studied febrile seizures in children with acute encephalitis/encephalopathy associated with fever, not with vaccines, Resp. Ex. YY at 4; Pet. Ex. 42;[179] *La Saux* and *von Spiczak* involved afebrile seizures, but the studies had limited value due to a lack of control group and unclear data entry, Tr. 149-50; Pet. Ex. 31; [180] Pet. Ex. 33;[181] *Scheffer* did not conclude that afebrile seizures can follow an MMR vaccine, Tr. 150-51; Pet. Ex. 58;[182] *Eckerle* was a case study of one child who had three tonic clonic seizures 6 days after MMR/varicella vaccines and the authors cautioned against assessing a causal relationship, Resp. Ex. YY at 4; Pet. Ex. 41;[183] *Weibel* discussed children who developed encephalopathy of no determined cause within 15 days of MMR based on passive surveillance with no control group and

[175] Davis & Barlow, *supra* note 28.
[176] Barlow et al., *supra* note 29.
[177] Demicheli et al., *supra* note 30. This is the article that Dr. Holmes referred to as the "Cochrane Review."
[178] It does not appear that this article was filed.
[179] Ichiyama et al., *supra* note 15.
[180] Le Saux et al., *supra* note 34.
[181] von Spiczak et al., *supra* note 35.
[182] Scheffer, *supra* note 87.
[183] Eckerle et al., *supra* note 49.

found a clustering with peak onset 8 and 9 days after immunization; there was no encephalopathy in this case, Resp. Ex. YY at 4; Pet. Ex. 45;[184] and finally, he argued that vaccine package insert lists of Adverse Reactions are not indicative of causation. Tr. 157-58, 172.

Dr. Holmes concluded that there is no evidence that the MMR vaccine or any vaccine can cause afebrile seizures or epilepsy. Tr. 152, 156, 160-161; Resp. Ex. A at 7; Resp. Ex. Q at 3; Resp. Ex. YY at 4.

Dr. McCusker described how the immune system responds to vaccines and infections by releasing low levels of cytokines into the peripheral circulation of the body, a process that is occurring constantly at low levels in the body. Tr. 186-188. Cytokines remain at low levels in the peripheral immune system, even when accompanied by a fever or a febrile seizure. Tr. 189-91, 197-99; Resp. Ex. GG.[185] She added that low level circulating peripheral cytokines do not have unfettered access to the CNS but can influence cytokine expression on the brain through communication molecules. Tr. 192, 205-06. However, excessive amounts of IL-1b are required to lower seizure threshold. Tr. 194-95. Thus, cytokines in the periphery following vaccination are not near the level necessary to reach the CNS, lower the seizure threshold, and cause seizures. Tr. 212.

Further, there is no support for petitioner's proposition that cytokines enter the brain, even in children with febrile seizures. Tr. 197-99; Resp. Ex. GG.[186] *Lin* studied live measles infection (and a co-infection of HIV-1) showing that IL-1b even at the time of rash maxed out at a very low level. Tr 202-03; Resp. Ex. HH.[187] The cytokine level would be even lower with a vaccine. *Id.* Further, animal studies show that an increase in peripheral IL-1b in a person predisposed to developing seizures is associated with a *down*regulation of the risk of seizures. Tr. 204. *Li* and *Vezzani* showed that IL-1b released in the brain after trauma, damage, or infection acts to repair damage to the brain. Tr. 210-11; Resp. Ex. RR;[188] Resp. Ex. SS.[189]

Dr. McCusker explained that it would take massive, excessive amounts of IL-1b to lower seizure threshold. Tr. 194-95, 208; *see* Resp. Ex. QQ.[190] Further, *Dubé* showed that—in addition to massive amounts of IL-1b injected directly into an animal's brain—hyperthermia had to be induced to lower seizure threshold. Tr. 194-95; Resp. Ex. QQ.[191] Dr. McCusker conceded that she did not know the exact amount of IL-1b necessary to lower the seizure threshold in a human, but she estimated it would be about a thousandfold the total amount of cytokines found in wild type measles infection. Tr. 234. She reached this conclusion based on *Dubé* and accounting for the size difference between mice and humans. Tr. 234. Regardless, cytokines in the periphery following vaccination are not at nearly high enough levels to lower seizure threshold and induce seizures. Tr. 212.

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[184] Weibel et al., *supra* note 50.
[185] Kashiwagi et al., *supra* note 53.
[186] *Id.*
[187] Lin et al., *supra* note 70.
[188] Li et al., *supra* note 57.
[189] Vezzani et al., *supra* note 138.
[190] Dubé et al., *supra* note 42.
[191] *Id.*

Dr. McCusker disagreed that receiving two live attenuated vaccines—MMR and Varicella—could "throw the IL-1b over the top," maintaining that IL-1b in the periphery would still be low. Tr. 213-14; *See* Resp. Ex. GG.[192] Further, high levels of cytokines in the body result in sickness, fever, marrow failure, kidney failure, and other serious symptoms. Tr. 216, 225. Dr. McCusker was unable to reconcile petitioner's theory that vaccines produce IL-1b at levels high enough to go beyond the periphery, breach the blood brain barrier, and trigger seizures. Tr. 197, 206-08. She explained when a vaccine is administered in the arm or leg, IL-1b is released to the draining lymph nodes, triggering nerve endings that signal up to the hypothalamus through the vagus nerve to increase body temperature to slow down and fight off the microbe giving the immune system the opportunity to get ahead of the microbial assault. Tr. 193, 205-06; Resp. Ex. GG.[193] She summarized that the circulating cytokines signal from the lymph node to the brain to change the body temperature, and the rise in temperature is what leads to the seizure. Tr. 195-96. *Kashiwagi* demonstrated that the IL-1b does not cause fever, but rather signals the lymph nodes to tell the brain to raise the body temperature. Tr. 196; Resp. Ex. GG.[194] "It's the fever that is inducing those seizures. It's not that IL-1b, in the brain, is inducing those seizures, and that's really a key element here, because we know from the febrile seizure story that circulating IL-1b is actually. . . undetectable in the *Kashiwagi* articles." Tr. 196; Resp. Ex. GG.[195]

Dr. McCusker noted that the timing for an inflammatory reaction following killed and live vaccines is different. Tr. 199-201. In killed vaccines, all cytokines—not just IL-1b—are transiently elevated, but still do not reach a high enough level to initiate an inflammatory event. Tr. 200. The cytokines are localized in the draining lymph node close to the vaccine site for the first two to three days, then the immune response circulates beyond the lymph nodes. Tr. 200. In a live vaccine, like the MMR or Varicella vaccines, the virus needs time to replicate so the response is not strong in the first several days. Tr. 200-01. After a few days, the immune response is activated to get control over the replicating virus. Tr. 201. The immune system then shuts down the virus by activating regulatory T cells. Tr. 227. Finally, 7-10 days after vaccination, the rash develops, indicating that the virus is under control, and the inflammatory cells are shutting down. Tr. 201, 227; Resp. Ex. FFF at 4. Further, the half-life for active peripherally circulating IL-1b is only 19 minutes. Tr. 215. After that, cytokines start to lose their activity significantly. Tr. 215.

In conclusion, Dr. McCusker stated the mechanism proposed in this case makes no biological sense and does not link the increase of IL-1b from vaccine(s) in the periphery to an afebrile seizure disorder. Tr. 221. Petitioner failed to explain how an inflammatory event that generated a normal immune response to the MMRV vaccines led to a change in the CNS. Tr. 224. The level of cytokines necessary to lower seizure threshold and cause seizures would be so significant, one would expect serious sick behaviors not an afebrile healthy child. Tr. 214, 225. From "a mechanistic standpoint, I can't put A and B together." Tr. 224.

Drs. Kinsbourne's and Levin's arguments, though forcefully presented, fail to provide any support for how vaccines administered on October 25, 2012 could cause afebrile seizures and epilepsy, regardless of whether those seizures began ten days or three weeks after vaccinations.

[192] Kashiwagi et al., *supra* note 53.
[193] *Id.*
[194] *Id.*
[195] *Id.*

In addition, Drs. Kinsbourne and Levin disagreed over what constituted the "two hits" in their theory— genetic propensity, birth trauma, neuronal damage or more—and whether it was the MMR vaccine or all the vaccines. Regardless their logic was circular: one event was caused by another simply because the second event occurred. The studies relied on discussed not only febrile seizures but the need for massive amounts of IL-1beta injected directly into animal brains with an induced fever to cause a seizure; neither occurred here. *See* Pet. Ex. 38;[196] Pet. Ex. 42.[197] Further, none of the literature provides a mechanism by which IL-1beta generated in the periphery as a normal immune response to vaccinations can cause afebrile seizures and damage to brain. Specifically, one of the studies relied on by petitioner concluded that "it is not possible based on these cases to assess a causal relationship between nonfebrile seizures and vaccination." Pet. Ex. 41.[198]

An important aspect of petitioner's causation theory is that fevers and seizures have separate pathways. However, petitioner never explained what exactly those "pathways" are. Dr. Levin merely pointed to *Dubé* and stated, "the fact of the matter is that this particular article says that cytokines cause seizures independent of fever." Tr. 101, 103; Pet. Ex. 38.[199] Not only was that a misinterpretation of the article, but it did little to aid in understanding petitioner's theory.

Notably, Dr. Kinsbourne described how pro-inflammatory cytokines, including IL-1b, signal the hypothalamus in the brain to generate fever and/or inflammation, and it is the fever or inflammation that generates a seizure in a susceptible person. Tr. 56-57. Dr. Kinsbourne's own testimony cannot be reconciled with his opinion here that IL-1b can cause a seizure without fever. Rather, this testimony proves the point that cytokines elicit fever, which in turn can cause seizures. There is no evidence that cytokines themselves, specifically IL-1b, can cause seizures without fever.

Neither Dr. Kinsbourne nor Dr. Levin explained how afebrile seizures could occur in excess of week or more after vaccination. Dr. Levin claimed that the November 2, 2012 rash was indicative of an inflammatory response that released cytokines which then led to seizures. Even accepting petitioner's theory that cytokines were released at the time of the rash, petitioner provided no explanation for how those cytokines stayed active for days and at such a high level as to cause seizure activity without fever "within two weeks" of the rash, given their half-life of only 19 minutes. *See* Tr. 215; Resp Ex. FFF at 4; Resp. Ex. HHH.[200] Further, petitioner failed to persuasively explain how cytokines themselves could result in afebrile seizures.

It is undisputed that febrile seizures can occur within 5-15 days after an MMR vaccine; this is recognized as an on-Table vaccine related injury. However, there is no support for petitioner's theory that MMR, Varicella, or any other vaccine can cause seizures in the absence of fever, edema, or encephalitis 10 or more days after vaccination. In rare cases where seizures occur following vaccination, pro-inflammatory cytokines lead to a fever, and the fever causes a seizure in a susceptible individual. As persuasively explained by respondent's experts, there is no

[196] Dubé et al., *supra* note 42.
[197] Ichiyama et al., *supra* note 15.
[198] Eckerle et al., *supra* note 49 at 3.
[199] Dubé et al., *supra* note 42.
[200] Kudo et al., *supra* note 81.

convincing evidence that vaccines can cause seizures in the absence of a fever or that vaccines can cause epilepsy.

Petitioner failed to satisfy Prong I.

B. *Althen* Prong Two: Petitioner Has Not Provided a Logical Sequence of Cause and Effect

Having determined that petitioner failed to satisfy *Althen* Prong I, it is unnecessary to discuss *Althen* Prongs II or III. *Veryzer v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 344 (2011); *see also* § 11(c)(1)(C)(ii). Nonetheless, I will discuss petitioner's evidentiary showing for Prongs II and III.

Dr. Kinsbourne opined that A.L.M. had a low seizure threshold due to genetic susceptibility, and thus, did not require a fever in order to have a seizure. Tr. 57, 78. Here, the MMR and/or Varicella vaccine(s) caused the release of cytokines, specifically IL-1b in a genetically susceptible child which caused afebrile seizures; if not for the vaccine(s), A.L.M. may have never developed seizures. Tr. 52, 82; Pet. Ex. 14 at 6-7.

Dr. Levin opined that A.L.M. had a low seizure threshold as result of brain trauma, including birth trauma and head trauma from two falls, rendering her susceptible to developing seizures. Tr. 121, 126-27. The cytokines evoked by the vaccines, specifically IL-1b, caused neuronal damage, which then led to A.L.M.'s afebrile seizures. Tr. 118; Pet. Ex. 39 at 2. All 21 separate infectious antigens and adjuvants A.L.M. received caused her seizures. Tr. 119-20; Pet. Ex. 39 at 1. Further, the rash that occurred on November 2 was consistent with a cytokine-induced inflammatory cutaneous reaction. Pet. Ex. 39 at 2; Pet. Ex. 50 at 1. Dr. Levin was the only expert to place any significance on the rash.

Dr. Holmes disagreed that A.L.M.'s neurological condition was vaccine related. Resp. Ex. Q at 3. He maintained that there was no proof that A.L.M.'s immune response resulted in neurological injury. Resp. Ex. YY at 3. In determining that A.L.M. had a normal immune response to the vaccinations, he noted that in the days and weeks following her vaccinations, A.L.M. had no sickness behavior, no fever, and no signs of an inflammatory reaction that could cause brain damage and seizures. Her MRIs were also normal. Tr. 158-59, 164-65; Resp. Ex. YY at 3.

In Dr. Holmes opinion A.L.M.'s course would have been the same, with or without the vaccine(s), because she had idiopathic epilepsy. Tr. 155-56, 162. Further, A.L.M. had many febrile illnesses before her vaccines and in the months that followed but did not have seizures. Tr. 162-63. This indicated that her seizures were simply related to the fact that she had epilepsy. Tr. 162. Given her family history and clinical course, the vaccines administered on October 25, 2012 were just a coincidence with the onset of seizures. Tr. 162-63. He submitted that her seizures were a result of individual genetic propensity, timing, and the stage of brain development—not vaccines. Tr. 161. "A.L.M. had a genetic epilepsy that was treated effectively and went into remission and is now doing well. There is no reason whatsoever to implicate any vaccine to her clinical course." Tr. 159-60.

Dr. McCusker found it noteworthy that A.L.M. had afebrile seizures which were not exacerbated by subsequent febrile events or infections. Resp. Ex. Z at 5. She explained that, even assuming the November 2 rash was vaccine related, A.L.M.'s cytokine levels from vaccination would be far below what would be necessary to lower her seizure threshold. *Id.* If there were high enough levels of cytokines to lower her seizure threshold as proposed by petitioner's experts, A.L.M. would have experienced sickness behaviors. Tr. 225. However, she was asymptomatic, afebrile, and otherwise healthy. Tr. 225. A.L.M. did not fit the picture of child with rampant circulation of cytokines. Tr. 225. Further, petitioner's experts failed to explain how a normal immune response to vaccines led to changes in A.L.M.'s CNS. Tr. 224.

A.L.M. has a family history of seizures and epilepsy and she received multiple vaccinations on October 25, 2012. *See* Pet. Ex. 7 at 17; Pet. Ex. 10 at 82. On November 2, 2012, A.L.M. developed a rash that lasted for an hour to several hours but disappeared without treatment. Tr. 9-10, 21, 26-27. She had no fever and no sick behaviors. Tr. 21-22. Ten or more days after vaccination,[201] A.L.M. began to display chewing motions, then staring, then finger rubbing, then not responding to her name. Tr. 24-27; Pet. Ex. 1 at 2; Pet. Ex. 12. At a doctor's visit on November 26, 2012, the pediatrician suspected that these behaviors reflected seizure activity. Pet. Ex. 11 at 115-16.

At all relevant times, A.L.M. was a healthy child. Other than a transitory rash, A.L.M.'s medical records and petitioner's testimony provided no indication that A.L.M. demonstrated any sick behaviors or fever at any point after her October 25 vaccinations or the onset of her afebrile seizures. Tr. 21-22. Further her MRIs were normal. Tr. 164-65; Pet. Ex. 10 at 64. Other than the onset of seizure activity, A.L.M. was afebrile and healthy at all times.

The medical records show petitioner to be diligent, cautious, and protective. She routinely called or visited the pediatrician whenever A.L.M. was sick. But the medical records are silent for the eight days between A.L.M.'s vaccinations and her November 2 rash and then silent again between the rash on November 2 and the November 26 doctor visit, indicating that A.L.M. did not display any sick behaviors, fever, or concerning behavior during that timeframe. Drs. Kinsbourne and Levin did not address the lack of sickness behaviors or fever in the days and weeks between her vaccination and onset of afebrile seizures. Only Dr. Levin placed any significance on A.L.M.'s November 2 rash, referring to it as a sign of excessive cytokines. Pet. Ex. 50 at 1. Even then, A.L.M. did not have a fever or demonstrate any sign of illness or high levels of cytokines. Tr. 21-22.

Notably, none of A.L.M.'s treating physicians related the onset of her afebrile seizures to her vaccinations.[202] Dr. Holmes, who specializes in the care and treatment of children with epilepsies, explained that epilepsy most commonly presents in children and is idiopathic most of the time. Tr. 131, 135-36; Resp. Ex. A at 7. A.L.M.'s family history supports the conclusion that her epilepsy was idiopathic. Petitioner herself has a history of seizures at the age of 3 and A.L.M.'s father has a half-brother with diagnosed epilepsy. Such evidence was more persuasive than Drs.

[201] Onset of symptoms will be more specifically addressed under Prong III.

[202] Other cases from the Vaccine Program have recognized that "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury," *Paluck*, 786 F.3d at 1385 (quoting *Andreu*, 569 F.3d at 1375).

Kinsbourne and Levin's statements to the contrary.

While medical literature and epidemiologic evidence is not required, it is still petitioner's burden to show that the vaccines she alleges to have caused injury can and did cause injury in her case. *See Althen*, 418 F.3d at 1282 (Fed. Cir. 2005); *Andreu*, 569 F.3d at 1380 (stating that the petitioner's burden in the Vaccine Program is preponderant evidence standard). The patchwork theory of causation woven by Drs. Kinsbourne and Levin does not provide a logical sequence of cause and effect between the vaccinations received and the onset of A.L.M.'s afebrile seizures and epilepsy. Petitioner has failed to provide proof that the MMR and/or Varicella and other vaccine(s) can cause and did cause A.L.M.'s afebrile seizures and epilepsy. Respondent's experts were more persuasive, and they demonstrated that A.L.M.'s afebrile seizures and epilepsy were unrelated to the vaccinations she received.

Petitioner failed to satisfy Prong II.

C. *Althen* Prong Three: Petitioner has Failed to Establish a Proximate Temporal Relationship

Resolution of Prong III requires that petitioner establish onset. It is undisputed that the medical literature supports onset of febrile seizures within 5 to 15 days following MMR vaccination. The Program recognizes that timeframe as reflected in the Vaccine Table. §300aa-14(a). However, as discussed at length above, there is no support for afebrile seizures following MMR or any vaccine, with the limited exception of those children who suffer from Dravet Syndrome. Tr. 147-49, 176; *See* Pet. Ex. 60.[203]

Based on the evidence presented, A.L.M.'s seizures began in excess of 15 days post vaccination. Petitioner was uncertain when the seizures began and used the November 2, 2012 rash as her frame of reference. She admitted to having to refer to the pediatric records and phone logs for the date the rash occurred. Tr. 21. Her best estimate of when the chewing began was within a week or two after the November 2 rash. Tr. 27-28. This would place onset between November 9 and November 16, or 15-22 days post vaccination. Petitioner then stated that the chewing started a few days after the rash, placing onset in the days between November 4 and November 6, or 10-12 days post-vaccination. Tr. 26. However, when petitioner presented A.L.M. to the pediatrician on November 26, 2012, she reported onset as a week prior, or roughly November 19, 26 days post-vaccination. Pet. Ex. 11 at 116. However, at the December 2, 2012 emergency room visit, petitioner reported onset of seizures as 4-6 weeks ago, placing onset around November 4 or October 21, two days after the rash or before vaccination. Pet. Ex. 15 at 2. Petitioner then clarified that when she reported symptoms starting 4-6 weeks prior, she was referring to the onset of the rash—not the seizures. Tr. 30-31. On December 3, 2012, petitioner reported seizure onset as one month prior, placing onset as one day after the rash and nine days post-vaccination. Pet. Ex. 7 at 171. On January 8, 2013, petitioner reported seizure onset as a month prior to December 2, 2012, placing onset on the day of the rash. Pet. Ex. 10 at 64. In October of 2013, petitioner reported the seizure onset as two weeks after vaccination. Pet. Ex. 5 at 24.

Two years after vaccination, petitioner filled out a VAERS report on October 15, 2014, in

[203] Cendes & Sankar, *Vaccinations and Febrile Seizures*, *supra* note 87.

which she reported that A.L.M. had a rash on her chest, neck, and face on November 2, 2012. Within two weeks, A.L.M. started making chewing motions and by the end of November, she was having staring spells. *See* Pet. Ex. 12. At hearing, petitioner agreed that she reported the onset of chewing motions as approximately two weeks after the November 2 rash, adding that things progressed quickly thereafter. Tr. 32-33.

Ms. Spencer submitted an affidavit that A.L.M. "broke out in a rash" on November 2, 2012. Pet. Ex. 17 at 1-2. However, at hearing she was unsure and believed the rash occurred either on November 7, 8, or 9. Tr. 40. The chewing motions and staring began a few days after the rash. Pet. Ex. 17 at 2; Tr. 40-41, 45-46. However, Ms. Spencer also testified that the family was together on Thanksgiving when the chewing motions, staring and finger rolling progressed and prompted an emergency room visit. Tr. 46-47. She later corrected herself, saying that they went to the emergency room on Christmas, not Thanksgiving. Tr. 47.

Ms. Mathison only briefly discussed symptom onset in her affidavit. She stated that A.L.M. began making chewing motions with nothing in her mouth and would rub her hands in November of 2012. Pet. Ex. 18 at 2.

A.L.M. received routine childhood vaccinations on October 25, 2012 seemingly without event. She developed a rash on November 2, 2012. The reporting of A.L.M.'s seizure onset was anywhere from 4 days prior to vaccination to one month post-vaccination. It is unclear whether petitioner's reference to "onset" at the emergency room on December 2, 2012 referred to the rash on November 2, 2012 or the chewing motions and staring. Two years after the events, petitioner prepared a VAERS report placing the onset of seizures as two weeks after the November 2, 2012 rash or roughly three weeks post-vaccination. For purpose of litigation, however, onset was alleged to be 2-4 days after the rash on November 2, 2012, or 10-12 days post-vaccination.

Dr. Kinsbourne opined that both MMR and Varicella vaccines, as live attenuated vaccines, have the same 5-to-15-day window for seizure onset during the period of viremia. Tr. 93-94. Based on the testimony he heard at hearing, Dr. Kinsbourne believed A.L.M. had her first seizure with facial movements 2-3 days after she developed a rash, or within the 5-to-15-day period. Tr. 54, 72. He acknowledged that both the VAERS report and the medical records suggest seizure onset two weeks after the November 2 rash. Tr. 85. Dr. Kinsbourne stated that if it was found that her seizures began in excess of two weeks after the MMR vaccine, the vaccine would ***not*** be responsible for her seizures. Tr. 85-86; Pet. Ex. 36 at 2. Thus, he stated that if the timeframe in the medical records rather than petitioner's testimony is accepted, the vaccine would not have been the cause of her seizures. Tr. 85.

Dr. Levin's opinion on onset was unclear. In his report, Dr. Levin stated that the first clinical signs of neuronal damage were the chewing motions, staring, not reacting to sound, and finger rubbing, which began within two weeks of vaccination. Pet. Ex. 39 at 2. He also stated that her seizures "were simply a further indication of the progression of neuronal damage and were noted one month later." *Id.* In the same report, he concluded that "her symptoms began within 2 weeks of the vaccination." *Id.* At hearing, he stated that the time between her vaccines and the afebrile seizures was approximately 10-14 days. Tr. 107.

Dr. Holmes agreed that febrile seizures can present between 7 to 14 days after MMR vaccination. Tr. 145-46; Resp. Ex. V at 2. He opined that there is no evidence that supports afebrile seizures resulting for vaccination. Tr. 146.

Dr. McCusker addressed onset of seizures being days after the November 2 rash, but she concluded that there would be no circulating cytokines after the rash resolved, so the seizures were unrelated. Tr. 227, 229; Resp. Ex. FFF at 4. She did, however, agree that the MMR vaccine can cause febrile seizures, although she did not specify the timeframe expected for onset of febrile seizures. Tr. 218-19.

There is no dispute that febrile seizures can occur within 5 to 15 days following MMR vaccine. Petitioner's experts argued that this timeframe applies to afebrile seizures as well, but they provided no literature to support this opinion. Respondent's experts disagreed, arguing instead that no vaccine can cause afebrile seizures, and certainly did not cause afebrile seizures here 10 or more days post-vaccination in an otherwise well child.

In summary, A.L.M. was a healthy child who received her routine vaccinations in the first year of life without event. On October 25, 2012, she again received routine vaccinations without event. On November 2 or eight days after vaccination, A.L.M. developed a transient rash while out shopping with her mother and aunt, which resolved within an hour to several hours without medical intervention. Tr. 9, 26-27. A.L.M. had no fever and no sickness behaviors. She subsequently developed chewing motions, staring, hand rubbing, and hand twitching at some point prior to being presented to the pediatrician on November 26, 2012. Tr. 24-26; Pet. Ex. 11 at 115-16. These episodes lasted for seconds, then she returned to baseline. Pet. Ex. 7 at 2. Petitioner took A.L.M. to the pediatrician on November 26, 2012, reporting onset as a week prior. Pet. Ex. 11 at 116. The pediatrician suspected that A.L.M. was having seizure activity. *Id.* She was ultimately diagnosed with idiopathic seizures and epilepsy, from which she has since recovered.

Assessing all the evidence submitted, the onset of A.L.M.'s afebrile seizures was at the very least 10 days after vaccination; more likely, though, her seizures began in excess of 15 days after vaccination as documented in the medical records. Petitioner is a diligent and protective mother. Based on the frequency of medical care reflected in the pediatric records, it is unlikely that petitioner would have waited over three weeks to take A.L.M. to the pediatrician if she had been displaying these behaviors. Thus, it is more likely that these behaviors began in late November 2012, shortly before or a week prior to petitioner taking A.L.M. to the pediatrician as she reported. Based on the medical records and petitioner, the onset of A.L.M.'s afebrile seizures was more than 15 days after the October 25, 2012 vaccinations and cannot be implicated as the cause. Petitioner's neurology expert, Dr. Kinsbourne, agreed that a vaccine could not be responsible if onset is deemed to be more than two weeks after vaccination. Tr. 85-86; Pet. Ex. 16 at 2; Pet. Ex. 36 at 2.

Therefore, petitioner failed to satisfy Prong III.

VIII. Conclusion

When petitioners fail to carry their burden, the Secretary is not required to present an alternate explanation for the vaccinee's condition. *De Bazan*, 539 F.3d at 1352. The petitioner in

this matter has failed to put forth a prima facie showing of causation and failed to demonstrate entitlement to compensation. This case must be dismissed.

In the absence of a timely filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accordance with this decision.[204]

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master

[204] Pursuant to Vaccine Rule 11 (a), if a motion for review is not filed within 30 days after the filing of the special master's decision, the clerk will enter judgment immediately.